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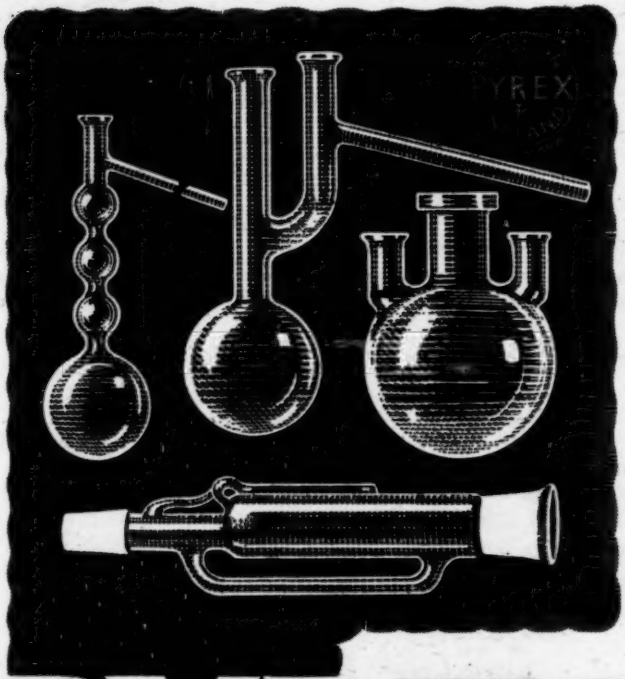

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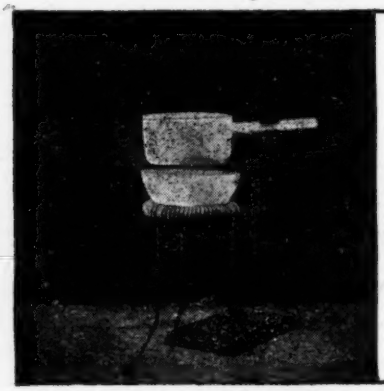

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agar, from which he infers that agar contains open-chain galactose units. Such units would, however, present the necessary grouping for attack by periodic acid irrespective of the carbon atom taking part in the linkage of the units. The stability of agar displayed in the experiments above described thus proves that open-chain galactose units cannot exist in the molecule and therefore some other explanation must be found for the formation of hepta-acetyl galactose.—UNIVERSITY COLLEGE, GALWAY. [*Received, November 14th*, 1941.]

The Autoxidisability of the Alkyl Groups in Xylene. By ERNEST HAROLD FARMER and ERIC S. NARRACOTT.

IN the course of early experiments on the oxidation of rubber it was observed that its solutions in commercial xylene when exposed at 75° to a stream of oxygen, in presence of acetic anhydride (added to accelerate reaction) and a cobalt catalyst, gave *m*- and *p*-toluic acid, together with neutral liquids which were clearly not derived from the rubber. For instance, when a solution of 675 g. of rubber in 6075 g. of xylene was mixed with 844 c.c. of acetic anhydride and 42 g. of cobalt naphthenate, and the mixture (in 4 batches) treated at 75° for 2 days with a stream of oxygen, there were obtained, respectively, (1) by extraction of the xylene solution with 10% caustic alkali and (2) by subsequent distillation at *ca.* 1 mm. pressure of the volatile material from the residual xylene liquor, about 10 g. of crystalline acid and 80 g. of volatile neutral oxidation products. The acid was toluic acid (Found: C, 70·6; H, 6·1; equiv., 135. Calc. for $C_8H_8O_2$: C, 70·55; H, 5·95%; equiv. 136), from which samples of both the *m*- and the *p*-isomeride (m. p. 110° and 176°, respectively) were isolated by fractional crystallisation. The neutral products when fractionally distilled gave: (*a*) aldehydic material, b. p. 85—87°/15 mm. (21 g.); (*b*) aldehydic material, b. p. 87—105°/15 mm. (13 g.); (*c*) alcoholic material, b. p. 105—108°/15 mm. (41 g.); and (*d*) neutral material, b. p. >108°/15 mm. (5 g.). Fraction (*a*) was nearly pure tolualdehyde (Found: C, 61·3; H, 6·15. Calc. for C_8H_8O: C, 61·0; H, 6·25%) and gave at once a mixture of isomeric semicarbazones, m. p. 205°; also it gave on oxidation with excess of boiling alkaline permanganate an 80% yield of mixed phthalic acids (Found: C, 58·0; H, 3·55. Calc. for $C_8H_6O_4$: C, 57·8; H, 3·65%). From the methyl ester derived from the mixed acids, methyl terephthalate, m. p. 139°, and methyl *iso*phthalate, m. p. 65°, were easily separated. Fraction (*c*), doubtless consisting of impure tolyl alcohols (Found: C, 75·4; H, 7·7. Calc. for $C_8H_{10}O$: C, 78·65; H, 8·25%), gave on oxidation with boiling permanganate good yields of mixed phthalic acids, resolvable after esterification into the *m*- and the *p*-isomeride.

When xylene (200 c.c.) containing no dissolved rubber was similarly oxidised for 1 day at 75° in presence of cobalt naphthenate (1 g.) and acetic anhydride (25 c.c.) there was obtained a quite similar mixture (14·5 g.) of the liquid and the acid oxidation products.

This oxidation of xylene, which is facilitated by the cobalt catalysts employed, doubtless proceeds *via* the hydroperoxide, $CH_3{\cdot}C_6H_4{\cdot}CH_2{\cdot}OOH$.—IMPERIAL COLLEGE OF SCIENCE AND TECHNOLOGY, LONDON, S.W. 7. [*Received, October 18th*, 1941.]

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31. Cannabis Indica. *Part IX. The Isolation of 3′ : 4′ : 5′ : 6′-Tetrahydrodibenzopyran Derivatives from Pulegone–Orcinol and Pulegone–Olivetol Condensation Products. Synthesis of* d-*Tetrahydrocannabinol.*

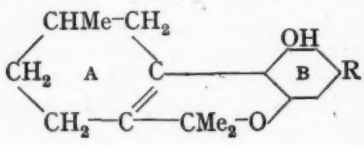
By G. LEAF, A. R. TODD, and S. WILKINSON.

Extension of the work described in Part VI (J., 1941, 137) has led to the isolation from the pulegone–orcinol condensation product of 6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (I; R = Me) as its crystalline acetate. The isolated phenol is dextrorotatory, but partial racemisation must have occurred at some stage, since the rotation is much lower than that of the pure *d*-form of (I; R = Me), whose synthesis is described. The nature of the resin accompanying (I; R = Me) in the condensation product remains to be determined. In the same way a dextrorotatory tetrahydrocannabinol (I; R = *n*-C_5H_{11}) has been isolated as an *l*-menthoxyacetate from the pulegone–olivetol product. For purposes of comparison *d*-tetrahydrocannabinol (I; R = *n*-C_5H_{11}) has been synthesised; it shows much less hashish activity in rabbits than does the racemic form.

THE view that some of the typical constituents of *Cannabis* resin might arise in nature by the condensation of terpene derivatives with dihydric phenols was expressed in earlier communications from these laboratories (Jacob and Todd, *Nature*, 1940, **145**, 350; J., 1940, 649) and investigations were then initiated with the object of realising such condensations in the laboratory. Condensations of pulegone with orcinol and with olivetol have already been reported (Part VI; Ghosh, Todd, and Wright, J., 1941, 137). These gave rise to resins which, on evidence derived from analysis, measurements of absorption spectra, behaviour on dehydrogenation, and, in the case of the olivetol product, pharmacological activity, were considered to be mixtures containing in each case about 50% of the expected tetrahydrodibenzopyran derivatives (I; R = Me) and (I; R = *n*-C_5H_{11}). Since the publication of these results Adams, Smith,

and Loewe (*J. Amer. Chem. Soc.*, 1941, **63**, 1973) have described very similar condensations and their results may be regarded as, in the main, confirmatory. The main difference between their results and our own is the pronounced *dextro*-rotation of their pulegone–olivetol product. This discrepancy may have been due to a variable amount of racemisation during our condensation or to some error in our original determination; at any rate, in subsequent experiments we have found the pulegone–olivetol product to show an optical activity similar in degree to that reported by these authors. The publication by Adams and his co-workers on this subject, however, makes it desirable for us to record some further results at this stage.

Definite proof of the correctness of our view as to the nature of one of the pulegone–orcinol products has been obtained by the isolation, from the acetylated resin, of 6″-acetoxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran. The identity of this substance, which has a pronounced *dextro*-rotation, was established by mixed m. p. determinations with an authentic specimen of the racemic modification (Ghosh, Todd, and Wilkinson, J., 1940, 1121) and by its hydrolysis to (I; R = Me). The product (I; R = Me) isolated in this way had $[\alpha]_D^{20°}$ approx. + 42° in successive preparations. That partial racemisation had occurred during the condensation was proved by synthesis of pure *d*-6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran (I; R = Me) in the following way. *d*-Methyl*cyclo*hexan-3-one, prepared from pulegone by heating with water under pressure (Wallach, *Annalen*, 1896, **289**, 340), was converted by the glyoxylic ester route into ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate. From this product, presumably containing a mixture of stereoisomers, *d*-5-hydroxy-5′ : 7-dimethyl-3 : 4-*cyclo*hexenocoumarin was obtained by condensation with orcinol in presence of sulphuric acid, and from it (I; R = Me) was prepared by a Grignard reaction; it had $[\alpha]_D^{20°} = +161°$.



(I.)

After separation of the acetate of (I; R = Me) from the acetylated pulegone–orcinol condensation product the residual resin was hydrolysed. Neither the resin so obtained nor any derivative of it has yet been crystallised. It has a definite *dextro*-rotation and analysis shows that it has the same composition as (I; R = Me). In alcoholic solution it shows selective light absorption at 2780 A. similar to, but a good deal less intense than, that shown by (I; R = Me). The possibility of its containing a double bond conjugated with an aromatic nucleus cannot be entirely excluded on this evidence, since there are indications of fairly intense absorption in the region of 2300 A.; this absorption band is more clearly evident in the acetylated resin. It may be mentioned that all the 3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyrans so far examined by us show strong light absorption between 2000 and 2300 A.; as a rule we have not recorded the intensity of absorption in this region, as it is difficult to measure accurately with the apparatus at our disposal and variation in intensity and location with different substituents is more easily followed in the maxima at higher wave-lengths. In Part VI (*loc. cit.*) it was suggested that the pulegone–orcinol condensation product might contain in addition to (I; R = Me) an isomer in which the double bond in ring A was not conjugated with the aromatic nucleus. The implied migration of a double bond during reaction has been criticised by Adams, Smith, and Loewe (*loc. cit.*) on the ground that it is without precedent; such criticism appears to us ill-considered in view of the numerous cases of deconjugation recorded in the literature, *e.g.*, the isomerisation of α-phellandrene to a mixture of α- and γ-terpinenes by means of sulphuric or phosphoric acid (Wallach, *Annalen*, 1887, **239**, 44; Carter, Smith, and Read, *J. Soc. Chem. Ind.*, 1925, **44**, 543). That the material accompanying (I; R = Me) should differ only in the location of a double bond now seems to us less probable, since not only does the crude pulegone–orcinol product give on catalytic dehydrogenation a poor yield of 6″-hydroxy-2 : 2 : 5′ : 4″-tetramethyldibenzopyran, but the residue after removal of (I; R = Me) gives on similar treatment a resin from which no crystalline product has been isolated. Several hypothetical structures, including some with angular alkyl groups, might be advanced for the resin, but no convincing evidence can at present be adduced in support of any one. Further investigation of this material is in hand; products rather similar in properties have also been obtained by condensing resorcinol derivatives with other terpene derivatives, *e.g.*, limonene and α-terpineol.

The isolation of (I; R = Me) from the pulegone–orcinol product made it practically certain that the pulegone–olivetol product must contain the tetrahydrocannabinol (I; R = *n*-C_5H_{11}). The lack of any crystalline derivative of (I; R = *n*-C_5H_{11}) at first hampered isolation efforts, but this difficulty was removed when it was discovered, in the course of some experiments on optical resolution, that synthetic racemic tetrahydrocannabinol (I; R = *n*-C_5H_{11}) yields a crystalline ester on treatment with *l*-menthoxyacetyl chloride. The product from the racemic phenol had m. p. 56—57°, whereas that from pure *d*-tetrahydrocannabinol (I; R = *n*-C_5H_{11}) synthesised from *d*-methyl*cyclo*hexan-3-one in a similar fashion to the

d-form of (I; R = Me), had m. p. 76—77°. Accordingly the distilled pulegone–olivetol product was esterified by means of *l*-menthoxyacetyl chloride, and the esterified material after purification by chromatographic analysis crystallised in part from alcohol. The crude crystalline product had m. p. 66—68°, raised by admixture with d-*tetrahydrocannabinol* l-*menthoxyacetate*. Presumably the pulegone–olivetol product contained partially racemised tetrahydrocannabinol, leading to the production of a mixture of *l*-menthoxyacetates. This mixture apparently underwent separation on further recrystallisation, since it yielded finally a product, m. p. 76°, undepressed on admixture with *d*-tetrahydrocannabinol *l*-menthoxyacetate and having an optical rotation only a little less than that of the latter. As regards the nature of the material accompanying tetrahydrocannabinol in the pulegone–olivetol product little further can be said than that it resembles closely the unidentified pulegone–orcinol product.

In the Gayer test on rabbits synthetic *d*-tetrahydrocannabinol (I; R = n-C_5H_{11}) appeared to show no activity in doses less than 6—8 mg./kg., *i.e.*, it was only $\frac{1}{3}$—$\frac{1}{4}$ as potent as the racemic modification. The pure *l*-form has not yet been obtained, but from these results it may be inferred that it should be 11—15 times as active as the *d*-form. Purified active fractions of hashish are lævorotatory, as also are the tetrahydrocannabinols obtained by cyclisation of cannabidiol (Adams, Pease, Cain, and Clark, *J. Amer. Chem. Soc.*, 1940, **62**, 2402). Another point of interest emerging from pharmacological tests by Professor A. D. Macdonald and Mr. G. Woolfe is that the acetate of tetrahydrocannabinol exhibits the hashish activity of the free phenol; it may be first hydrolysed in the animal, however, since the action is slow in developing and is very prolonged.

Experimental.

Pulegone–Orcinol Condensation Products.—The condensation of pulegone with orcinol, carried out as described by Ghosh, Todd, and Wright (*loc. cit.*), gave a pale yellow resin distilling at 155—160° (bath temp.)/10^{-1} mm., $[\alpha]_D^{22°}$ + 47·1° (*c* = 0·956 in chloroform). Light absorption in alcohol: max. 2720 A.; ε, 3520. This resin was acetylated by heating with acetic anhydride in pyridine solution. The product distilled at 150—152°/10^{-1} mm. and had $[\alpha]_D^{22°}$ + 33·8° (*c* = 1·670 in chloroform). An alcoholic solution of this material slowly deposited colourless prisms (4 g.), m. p. 123° after recrystallisation from alcohol, $[\alpha]_D^{21°}$ + 30·4° (*c* = 2·076 in chloroform). Light absorption in alcohol: maxima at 3050 A. (ε, 4425), 2670 A. (ε, 7605) and 2250 A. (ε, 23,100). A mixed m. p. with *dl*-6″-acetoxy-2 : 2 : 5′ : 4″-tetramethyl-3′ : 4′ : 5′ : 6′-tetrahydrodibenzopyran [m. p. 124°; absorption maxima in alcohol 3050 A. (ε, 4680), 2670 A. (ε, 7550), and 2250 A. (ε, 24,000)] showed no depression. In a second pulegone–orcinol condensation the crude acetylated resin had $[\alpha]_D^{23°}$ + 40·0° (*c* = 1·474 in chloroform), and the isolated crystalline acetate $[\alpha]_D^{20°}$ + 30·6° (*c* = 1·270 in chloroform). Hydrolysis of this crystalline acetate gave (I; R = Me), m. p. 112°, $[\alpha]_D^{19°}$ + 42·7° (*c* = 2·273 in chloroform). Light absorption in alcohol: maxima at 2780 A. (ε, 8,930) and 2290 A. (ε, 24,000). A mixed m. p. with the synthetic *dl*-modification of (I; R = Me) [m. p. 113°; absorption maxima in alcohol: 2780 A. (ε, 10,600) and 2300 A. (ε, 25,500)] showed no depression.

The non-crystalline portion (16 g.) of the acetylated pulegone–orcinol product (20 g.) had $[\alpha]_D^{20°}$ + 23·2° (*c* = 4·866 in chloroform) and in alcoholic solution it showed maxima at 2650 A. (ε, 3680) and 2330 A. (ε, 8700). Hydrolysis with alcoholic potassium hydroxide yielded a colourless resin, $[\alpha]_D^{18°}$ + 36·8° (*c* = 1·276 in chloroform), which defied all efforts at crystallisation (Found: C, 79·0; H, 9·0. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%). On catalytic hydrogenation (PtO_2) 79·5 mg. absorbed 6·8 c.c. of hydrogen (calculated absorption for $C_{17}H_{22}O_2$ taking up 1 mol. of hydrogen, 6·8 c.c.). In a second preparation the non-crystalline portion of the acetylated resin had a higher dextrorotation, $[\alpha]_D^{23°}$ + 36·8° (*c* = 2·092 in chloroform).

d-*Methyl*cyclo*hexan*-3-*one*.—Pulegone (125 g.) and water (100 g.) were heated at 250° in an autoclave for 2 hours (Wallach, *loc. cit.*). The oil was separated, dried, and distilled, yielding *d*-methyl*cyclo*hexan-3-one (48 g.), b. p. 168—170°, $[\alpha]_D^{19·5°}$ + 7·9° (*c* = 5·928 in alcohol). The alternative method of preparation from pulegone with sulphuric acid (Zelinsky, *Ber.*, 1897, **30**, 1532) was found to be unsatisfactory.

d-5-*Hydroxy*-5′ : 7-*dimethyl*-3 : 4-cyclo*hexenocoumarin*.—Ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate ($[\alpha]_D^{19°}$ + 79·2°), prepared from *d*-methyl*cyclo*hexan-3-one, was condensed with orcinol in presence of concentrated sulphuric acid in the normal manner. The coumarin formed colourless needles, m. p. 252—253°, $[\alpha]_D^{18°}$ + 168·3° (*c* = 0·974 in alcohol). The corresponding *dl*-coumarin has m. p. 260° (Ahmad and Desai, *Chem. Abstr.*, 1938, 9066) and a mixture of the two melted at 253—255°.

d-6″-*Hydroxy*-2 : 2 : 5′ : 4″-*tetramethyl*-3′ : 4′ : 5′ : 6′-*tetrahydrodibenzopyran* (I; R = Me).—Prepared from the above coumarin by the method of Ghosh, Todd, and Wilkinson (*loc. cit.*), the *product* crystallised from light petroleum in colourless plates, m. p. 104—105°, $[\alpha]_D^{19·7°}$ + 161° (*c* = 1·684 in chloroform) (Found: C, 78·8; H, 8·4. $C_{17}H_{22}O_2$ requires C, 79·1; H, 8·5%). In alcoholic solution it showed absorption maxima at 2785 A. (ε, 10,600) and 2300 A. (ε, 25,500). The corresponding racemic compound has m. p. 113° and a mixed m. p. of the two was 106—110°.

d-5-*Hydroxy*-5′-*methyl*-7-n-*amyl*-3 : 4-cyclo*hexenocoumarin*.—Prepared as above from optically active ethyl 1-methyl*cyclo*hexan-3-one-4-carboxylate and olivetol, the coumarin had a rather indefinite m. p. 145—

148°; $[\alpha]_D^{24°}$ + 130·3° (*c* = 2·34 in chloroform). The corresponding racemate has m. p. 177° (Ghosh, Todd, and Wilkinson, *loc. cit.*). The *acetate* had m. p. 76—77° and $[\alpha]_D^{22°}$ + 132·9° (*c* = 0·948 in chloroform) (Found: C, 73·8; H, 7·8. $C_{21}H_{30}O_4$ requires C, 73·7; H, 7·6%). The mixed m. p. with the racemic acetate (m. p. 82—83°) was 78—79°.

d-*Tetrahydrocannabinol* (I; R = *n*-C_5H_{11}).—Prepared by the action of methylmagnesium iodide on the above acetoxycoumarin, the *product* was a purplish resin distilling at 160° (bath temp.)/10^{-3} mm. (Found: C, 79·8; H, 9·6. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·5%). It had $[\alpha]_D^{20°}$ + 134·8° (*c* = 0·331 in chloroform) and in alcoholic solution had absorption maxima at 2750 A. (ε, 11,500) and 2290 A. (ε, 25,120).

d-Tetrahydrocannabinol *l*-menthoxyacetate, prepared from *d*-tetrahydrocannabinol by heating with *l*-menthoxyacetyl chloride (Read and Grubb, *J. Soc. Chem. Ind.*, 1932, **51**, 330T) in pyridine solution, crystallised from 95% alcohol in colourless needles, m. p. 76—77°. It had $[\alpha]_D^{25°}$ + 62·16° (*c* = 0·708 in chloroform) and in alcoholic solution showed absorption maxima at 3050 A. (ε, 5500), 2690 A. (ε, 8160), and 2260 A. (ε, 23,000).

l-*Menthoxyacetate of* dl-*Tetrahydrocannabinol.*—Menthoxyacetylation of racemic (I; R = *n*-C_5H_{11}) gave an *ester* crystallising from 95% alcohol in colourless needles, m. p. 56—57° (Found: C, 77·5; H, 9·8. $C_{33}H_{50}O_4$ requires C, 77·6; H, 9·8%). It had $[\alpha]_D^{17·5°}$ − 53·7° (*c* = 0·670 in chloroform) and its absorption spectrum in alcohol showed maxima at 3050 A. (ε, 5360) and 2700 A. (ε, 8330). The mixed m. p. with *d*-tetrahydrocannabinol *l*-menthoxyacetate (m. p. 76—77°) was 68—72°.

Pulegone–Olivetol Condensation Products.—Repetition of the pulegone–olivetol condensation as described by Ghosh, Todd, and Wright (*loc. cit.*) gave products which, contrary to the statement made in that communication, had a pronounced dextrorotation. The following account refers to the product from one such condensation, a pale yellow resin distilling at 160—170° (bath temp.)/6 × 10^{-3} mm.; it had $[\alpha]_D^{21°}$ + 62·7° (*c* = 2·976 in chloroform). After three further distillations the main fraction, b. p. 140—142° (bath temp.)/1·5 × 10^{-5} mm., had $[\alpha]_D^{21°}$ + 76·5° (*c* = 2·104 in alcohol). In agreement with earlier observations this material showed an absorption maximum in alcohol at 2780 A. (ε, 5340). A portion of the resin (450 mg.) was refluxed with *l*-menthoxyacetyl chloride in pyridine and the product, a reddish viscous oil, was dissolved in light petroleum and adsorbed on a column of activated aluminium oxide (2 cm. × 20 cm.; Birmingham Electric Co., Ltd.). When the column was washed with light petroleum (250 c.c., b. p. 40—60°) and the washings were evaporated, a colourless resin (*ca.* 300 mg.) was obtained which on dissolution in a small amount of alcohol and standing in the ice-chest for 24 hours deposited a crystalline menthoxyacetate, m. p. 66—68°. After three recrystallisations from alcohol this product was obtained in colourless needles (80 mg.), m. p. 76°, undepressed on admixture with *d*-tetrahydrocannabinol *l*-menthoxyacetate (m. p. 76—77°) (Found: C, 77·5; H, 10·0. Calc. for $C_{33}H_{50}O_4$: C, 77·6; H, 9·8%). It had $[\alpha]_D^{24°}$ + 51·9° (*c* = 0·616 in chloroform) and in alcoholic solution showed absorption maxima at 3050 A. (ε, 5360) and 2710 A. (ε, 8460). Hydrolysis of this ester gave a tetrahydrocannabinol having $[\alpha]_D^{29·4°}$ + 118·4° (*c* = 1·09 in chloroform).

The mother-liquor from the original crystallisation yielded on evaporation a colourless resin (*ca.* 200 mg.), $[\alpha]_D^{23·4°}$ − 31·4° (*c* = 2·506 in chloroform). On hydrolysis a dextrorotatory resin was obtained, b. p. 155° (bath temp.)/3·8 × 10^{-4} mm., $[\alpha]_D^{22°}$ + 59·2° (*c* = 1·39 in alcohol), closely resembling the original pulegone–olivetol product in its light absorption (ε, 5055 at 2760 A.). By eluting with benzene the material remaining on the adsorbent after the above-mentioned chromatogram had been washed with light petroleum, a product was obtained, which was hydrolysed to a pale yellow resin, $[\alpha]_D^{22°}$ + 22·2° (*c* = 1·17 in alcohol), with a rather similar absorption spectrum (ε, 3050 at 2790 A.).

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THE UNIVERSITY OF MANCHESTER. [*Received, November 18th*, 1941.]

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32. Cannabis Indica. *Part X. The Essential Oil from Egyptian Hashish.*

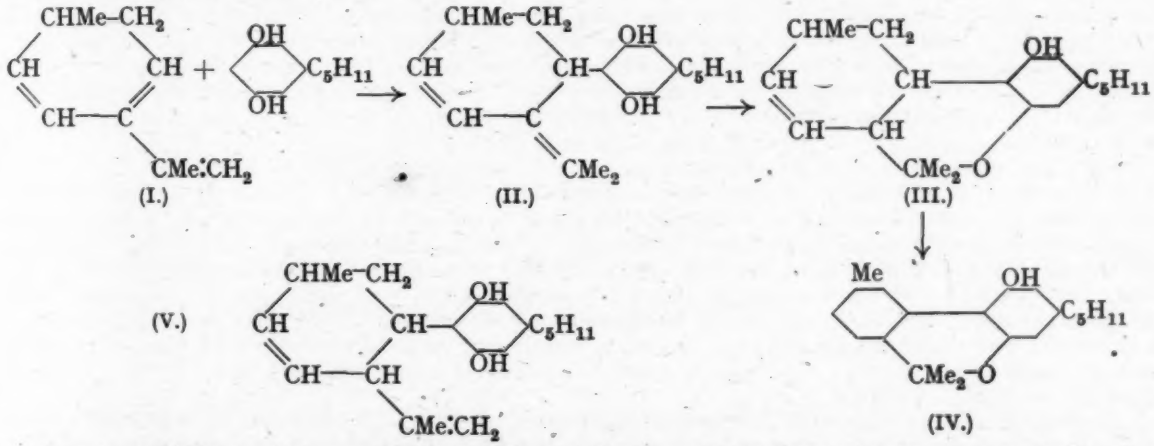
By J. L. SIMONSEN and A. R. TODD.

Examination of the essential oil from Egyptian hashish shows that the lower-boiling "terpene fraction" consists mainly of *p*-cymene with small amounts of 1-methyl-4-*iso*propenylbenzene and unidentified optically active material. From the higher-boiling fraction of the oil, humulene (α-caryophyllene) has been isolated. A hypothetical scheme for the biogenesis of cannabinol and related compounds is discussed in the light of these findings.

IT has long been known that *Cannabis* resin contains a considerable proportion of material, generally described as the "terpene fraction," which is devoid of hashish activity and boils at considerably lower temperatures than the active "crude cannabinol." The only recorded examination of it was made by Wood, Spivey, and Easterfield (J., 1896, **69**, 539), who reported the separation from it of a terpene, b. p. 165—175°, possibly myrcene, and a sesquiterpene. A renewed examination of the low-boiling constituents

of the resin was particularly desirable in view of the suggestion made in earlier papers of this series that some of the typical constituents of hemp resin, *e.g.*, cannabidiol and cannabinol, owe their origin in nature to terpene–phenol condensations. In the course of his investigations on cannabinol (J., 1930, 986; 1931, 630; 1932, 1342; 1933, 1400) Cahn accumulated a quantity of the lower-boiling oils from Egyptian hashish. We have been fortunate in having this material placed at our disposal in the form of two fractions, described as "low boiling" and "high boiling terpenes"; these oils have now been examined with the following results.

The "low boiling terpene" fraction consisted mainly of *p*-cymene in admixture with an unidentified optically active constituent and 1-methyl-4-*iso*propenylbenzene. The last-named substance was identified by oxidation to *p*-tolyl methyl ketone, characterised by preparation of its semicarbazone and 2 : 4-*dinitrophenylhydrazone*. In addition to terephthalic and 4-*iso*propenylbenzoic acids derived from *p*-cymene, oxidation of various fractions of the oil gave succinic and lævulic acids; these were probably derived from the unidentified optically active constituent. Contrary to the findings of Wood, Spivey, and Easterfield (*loc. cit.*) no myrcene was detected. Its absence may have been due to the fact that the oil examined by us was prepared some years ago from Egyptian hashish of uncertain age, since myrcene is known to polymerise readily. 1-Methyl-4-*iso*propenylbenzene does not appear to have been found previously in nature, and its occurrence in hashish is of some interest in connection with the biogenesis of compounds related to cannabinol. A reasonable, if entirely speculative, scheme for the biogenesis of cannabinol is given below in formulæ (I) to (IV). All the reactions involved would appear to be within the normal compass of plant metabolism.



Structure (II), derived from condensation of a menthatriene (I) with olivetol, differs only in the location of one ethenoid linkage from that (V) proposed by Adams, Loewe, Pease, Cain, Wearn, Baker, and Wolff (*J. Amer. Chem. Soc.*, 1940, **62**, 2566) for cannabidiol, and indeed is identical with the structure formerly envisaged by us on the basis of the absorption spectrum of that compound. A compound of structure (V), of course, could hardly be produced by this type of mechanism without some secondary rearrangement. It may, however, perhaps be pertinent to recall here that the *iso*propenyl–*iso*propylidene change can occur under conditions such as would suggest that the two structures may in a sense be regarded as tautomeric (cf. Bradfield, Penfold, and Simonsen, J., 1935, 311). The position of the cyclic ethenoid linkage in cannabidiol (V) is not known with any certainty. Structure (III) probably represents one of the tetrahydrocannabinols produced on cyclisation of cannabidiol by acidic reagents. All available evidence suggests that the active fractions of hashish contain a mixture of tetrahydrocannabinols; these in all probability include the cyclised isomerides of cannabidiol. Dehydrogenation of (III) would yield cannabinol (IV). A menthatriene (I) could, of course, very readily yield by isomerisation *p*-cymene, or by dehydrogenation 1-methyl-4-*iso*propenylbenzene. The fact that these two compounds have been found to make up the bulk of the low-boiling "terpene fraction" of hashish is certainly not inconsistent with the formation of (I) as a phytosynthetic intermediate by the hemp plant, and in that sense lends colour to the speculative scheme outlined above.

From the higher-boiling "terpene fraction" a sesquiterpene was isolated and characterised as its nitrosochloride and nitrolpiperidide. It proved to be humulene (α-caryophyllene), hitherto found only in oil of hops and oil of cloves. Both the hop plant (*Humulus lupulus*) and hemp (*Cannabis sativa*) belong to the same botanical family (*Moraceæ*).

Experimental.

Low-boiling Terpene Fraction.—The pale brown oil used in these experiments had $d_{20°}^{20°}$ 0·8592, $n_D^{20°}$ 1·4863, and $[\alpha]_{5461}$ +17·8°. A quantity of the oil was systematically fractionated (6 times) through a Widmer column. The two final fractionations were made over sodium; more than 50% of the oil distilled between 170° and 185°, the following fractions being obtained:

No.	B. p. (765 mm.).	$d_{20°}^{20°}$.	$n_D^{20°}$.	$[\alpha]_{5461}$.	No.	B. p. (765 mm.).	$d_{20°}^{20°}$.	$n_D^{20°}$.	$[\alpha]_{5461}$.
1	140—150°	0·7894	1·4496	+ 6·3°	5	169—175°	0·8500	1·4782	+27·8°
2	150—157	0·8035	1·4576	+13·1	6	175—178	0·8506	1·4800	+21·9
3	157—165	0·8304	1·4672	+24·4	7	178—180	0·8592	1·4909	+16·2
4	165—169	0·8451	1·4748	+28·5	8	180—185	0·8609	1·4948	+12·2

Crystalline derivatives could not be prepared from any of these fractions, nor did they react with maleic anhydride. From fraction 7 a *monohydrochloride*, b. p. 110—120°/21 mm. (Found: Cl, 20·0. $C_{10}H_{17}Cl$ requires Cl, 20·5%), was prepared. All these fractions were treated with oxidising agents (ozone and potassium permanganate) in attempts to isolate a characteristic derivative of the optically active hydrocarbon (or hydrocarbons) present in the oil. These experiments were all unsuccessful, the results of three being outlined below.

(1) *Ozonolysis of fraction* 6 (*b. p.* 175—178°). The oil (5 c.c.) in methyl acetate was ozonised at 0°; much formaldehyde was present in the issuing gases (dimedone test). After removal of the solvent under diminished pressure the ozonide was mixed with water (5 c.c.) and decomposed by heating on the water-bath for 1 hour. The aqueous solution was made alkaline with sodium carbonate and kept overnight after the addition of hydrogen peroxide (20 vol.; 1 c.c.). The neutral oxidation product (A) was dissolved in ligroin (b. p. 40—60°), the alkaline solution acidified, and the liquid acid (1·4 g.) extracted with ether.

The neutral oil (A) reacted readily with semicarbazide acetate, yielding a semicarbazone crystallising in silky prismatic needles, m. p. 203—204° alone and in admixture with *p*-tolyl methyl ketone semicarbazone (Found: C, 63·3; H, 7·2. Calc. for $C_{10}H_{13}ON_3$: C, 62·8; H, 6·8%). The 2 : 4-*dinitrophenylhydrazone* prepared from the neutral oil or from *p*-tolyl methyl ketone crystallised from *cyclo*hexyl acetate in scarlet prismatic needles, m. p. 252—253° (Found: N, 17·7. $C_{15}H_{14}O_4N_4$ requires N, 17·8%).

The acidic oxidation product, which was a gum, was not further examined.

(2) *Oxidation of fraction* 5 (*b. p.* 169—175°) *with potassium permanganate.* The oil (13 g.), suspended in water (250 c.c.) containing potassium hydroxide (26 g.), was mixed with ice (750 g.) and solid potassium permanganate (65 g.) and shaken for 20 hours. The excess of permanganate was removed with sulphur dioxide, the neutral oil (A) distilled in steam, and the aqueous solution after removal of the manganese dioxide sludge concentrated, acidified, and extracted with ether. Evaporation of the dried extract gave a gum (3·5 g.), from which a solid slowly separated, identified as terephthalic acid. From the filtrate, after removal of the ether, a crystalline solid slowly separated; after trituration with hydrochloric acid it crystallised from dilute acetic acid in needles, m. p. 156—157°, identified as *p-iso*propenylbenzoic acid (Found: C, 74·5; H, 6·2. Calc. for $C_{10}H_{10}O_2$: C, 74·1; H, 6·2%).

The neutral oil (A) (5 c.c.) was distilled over sodium and had b. p. 172—174°/759 mm., $d_{20°}^{20°}$ 0·8556, $n_D^{20°}$ 1·4869, $[\alpha]_{5461}$ + 5·4°. It was oxidised with chromic acid as described by Linstead *et al.* (J., 1940, 1143) and gave terephthalic acid (2·75 g.), identified by the methyl ester, m. p. 140°. The percentage of *p*-cymene in this neutral oil is therefore approximately 72·7%.

(3) *Oxidation of fractions* 7 *and* 8 *with potassium permanganate.* The oil (55 g.) in acetone (200 c.c.), cooled in ice and mechanically stirred, was oxidised with potassium permanganate (150 g.). The manganese dioxide was separated, and the acetone removed from the filtrate, leaving an oil which on distillation at 754 mm. gave the following fractions: (i) b. p. 170—180°, mainly 175—176° (17·3 g.); (ii) b. p. 180—190° (5·8 g.); and (iii) b. p. 190—220° (2·5 g.). Fraction (iii) was practically pure *p*-tolyl methyl ketone, identified by the preparation of the semicarbazone and 2 : 4-dinitrophenylhydrazone. The same ketone was present also in small quantity in the two lower-boiling fractions, which, however, consisted essentially of *p*-cymene.

The manganese dioxide sludge was thoroughly extracted with hot water, and the aqueous solution concentrated, acidified, and extracted with ether in a constant extraction apparatus. This gave a liquid acid (20 g.), a considerable quantity of a resinous acid being insoluble in ether. The acid, which contained much acetic acid, reacted readily with carbonyl reagents and gave bromoform on mixing with sodium hypobromite. No crystalline derivatives could be prepared, the calcium and barium salts being soluble in water. The acid was esterified with methyl alcohol and sulphuric acid in the usual manner; the ester, on distillation under 18 mm., yielded the following fractions: (i) b. p. up to 100° (0·6 g.); (ii) b. p. 100—120° (1·7 g.); (iii) b. p. 120—140° (1·7 g.); (iv) b. p. 140—160°, mainly 155° (3·3 g.); and (v) b. p. 160—200° (2·5 g.).

Fractions (i) and (ii) reacted readily with 2 : 4-dinitrophenylhydrazine sulphate to yield a crystalline 2 : 4-dinitrophenylhydrazone, which separated from methyl alcohol in yellow needles, m. p. 131° alone and in admixture with methyl lævulate 2 : 4-dinitrophenylhydrazone (Found: C, 46·7; H, 4·2. Calc. for $C_{12}H_{14}O_6N_4$: C, 46·6; H, 4·2%).

The ester (2 g.) was hydrolysed with methyl-alcoholic potassium hydroxide and yielded by extraction with

ether a liquid acid which partially crystallised. The solid was collected and recrystallised from hydrochloric acid; it then had m. p. 182—183° and was identified as succinic acid. No crystalline acid could be separated from the filtrate. Oxidation of this crude acid with sodium hypobromite gave a further small amount of succinic acid.

Fraction (iii) gave a liquid 2 : 4-dinitrophenylhydrazone. Hydrolysis of the ester (1·6 g.) with methyl-alcoholic potassium hydroxide gave an acid (1·4 g.), from which a small quantity of *p-iso*propenylbenzoic acid was isolated, formed presumably by loss of water from the *tert.*-hydroxy-acid. The liquid acid was oxidised with sodium hypobromite in the usual manner, the acid so obtained (1·1 g.) depositing an amorphous solid identified as terephthalic acid by the preparation of the methyl ester, m. p. 140°.

Fractions (iv) and (v) behaved similarly to fraction (iii). The only oxidation acid which could be identified was terephthalic acid.

High-boiling "Terpene" Fraction.—This oil distilled at 110—130°/20 mm. as a faintly yellow oil which reacted with Brady's reagent to yield in small amount a red liquid 2 : 4-dinitrophenylhydrazone.

A quantity of the oil (66 g.) was digested with alcoholic potassium hydroxide (KOH, 10 g.) to remove any esters present and after recovery of the neutral oil in the usual manner this was distilled under diminished pressure (18 mm.), the following fractions being obtained: (i) b. p. up to 100° (11·7 g.); (ii) b. p. 100—110° (11·5 g.); (iii) b. p. 115—125° (10·9 g.); (iv) b. p. 125—145° (22·4 g.); and (v) b. p. above 145° (6·2 g.). The lower-boiling fractions were yellow; fractions (iv) and (v) were blue and evidently contained some azulene. Redistillation (at 25 mm.) gave (*a*) b. p. up to 100°, mainly 80° (14·8 g.); (*b*) b. p. 110—115° (7·9 g.); (*c*) b. p. 115—125° (6·2 g.); (*d*) b. p. 125—140°, mainly 133—135° (21 g.); and (*e*) above 140° (10 g.).

Fraction (*d*) was redistilled twice over sodium and obtained as a faintly yellow oil, b. p. 130—132°/20 mm., $d_{20^\circ}^{20^\circ}$ 0·8958, $n_D^{20^\circ}$ 1·4962, $[\alpha]_{5461}$ −8·2°, consisting apparently essentially of humulene (α-caryophyllene). The nitrosochloride, decomp. 168° after softening at 155°, crystallised from chloroform–alcohol in cubes, decomp. 174°, and yielded a nitrolpiperidide, crystallising from alcohol in plates, m. p. 145—146°, unchanged in admixture with humulene nitrolpiperidide. The oil gave a liquid hydrochloride and on dehydrogenation with selenium an azulene resulted which was not further examined. No naphthalene hydrocarbon was formed.

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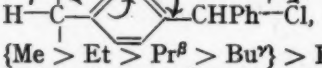
33. *Mechanism of Aromatic Side-chain Reactions with Special Reference to the Polar Effects of Substituents. Part XI. The Aldehydecyanohydrin Reaction: Evidence for the Mesomeric Effects of Alkyl Groups.*

By JOHN W. BAKER and (MISS) MABEL L. HEMMING.

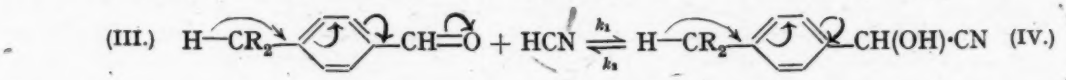
In the equilibrium (I) p-C_6H_4R·CHO + HCN $\underset{k_2}{\overset{k_1}{\rightleftharpoons}}$ p-C_6H_4R·CH(OH)·CN (II), where R = H, Me, Et, Pr^β, or Bu^γ, conjugation of the alkyl group, necessary for the operation of its mesomeric effect (Baker and Nathan, J., 1935, 1844), extends to the side-chain carbonyl group in (I), but is restricted to the benzene ring in (II). If this effect were predominant, stabilisation of the free aldehyde relative to its cyanohydrin should increase in the order H < Bu^γ < Pr^β < Et < Me. The values of the dissociation constant of the cyanohydrin $K = k_2/k_1$ have been determined in constant boiling-point alcohol at 20° and 35°, and both series follow the sequence K = Me > Et > Pr^β > Bu^γ > H, in agreement with the above expectations. The order is confirmed by the corresponding values of $\Delta F = -RT \ln K$, and the data thus provide the first conclusive evidence for an order of mesomeric electron-release Me > Et > Pr^β > Bu^γ. This, together with the evidence for the same order in the electromeric effect obtained by Hughes, Ingold, and Taher (J., 1940, 949), completes the experimental proof of the original hypothesis of Baker and Nathan (*loc. cit.*).

The values of k_1 and k_2 have also been determined at 20°, and these results, together with those relating to K, find a simple and consistent explanation on the basis of the changes in energy levels effected in the initial, transition, and final states of the reaction by the combined operation of the inductive and tautomeric effects of the alkyl substituents.

THE theory of partial conjugation of electrons of a C–H bond with an attached unsaturated system, H—$\overset{\curvearrowright}{C}$—$\overset{\curvearrowright}{C}$=$\overset{\curvearrowright}{C}$, postulated by Baker and Nathan (J., 1935, 1844) to explain the rate sequence {Me > Et > $Pr^\beta \approx Bu^\gamma$} > H for the bimolecular, nucleophilic substitution p-C_6H_4R·CH_2Br + C_5H_5N ⟶ p-C_6H_4R·CH_2·$\overset{+}{N}C_5H_5\}\overset{-}{Br}$, has since been conclusively verified by Hughes, Ingold, and Taher (J., 1940, 949) in the unimolecular solvolysis of p-alkylbenzhydryl halides. In this reaction the electron-

release by the tautomeric mechanism is of predominating importance in the transition state,  , and leads to a well-spaced sequence of velocity coefficients $\{Me > Et > Pr^{\beta} > Bu^{\gamma}\} > H$ supported by a corresponding differentiation in activation energies. This evidence, since it is derived from reaction kinetics, only proves the existence of an *electromeric* (polarisability) effect decreasing in the order $Me > Et > Pr^{\beta} > Bu^{\gamma}$ required by Baker and Nathan's hypothesis. Evidence so far obtained for a corresponding *mesomeric* (polarisation) effect (cf., *inter alia*, Davies and Hammick, J., 1938, 763; Davies, *ibid.*, p. 1865; Baker, Dippy, and Page, J., 1937, 1774; Baker, Nathan, and Shoppee, J., 1935, 1847; Baker, J., 1939, 1150; Baker and Nathan, J., 1936, 236; Burkhardt *et al.*, *ibid.*, pp. 17, 25, 1649, 1654), is inconclusive for one or other of the following reasons: (1) it refers only to incomplete series of alkyl groups, or (2) only partial inversion of the electron-release order $Bu^{\gamma} > Pr^{\beta} > Et > Me > H$, indicated by the inductive effects, has been realised. The object of the present communication is to provide equally conclusive evidence for an order of mesomeric electron-release $Me > Et > Pr^{\beta} > Bu^{\gamma} > H$.

It was considered that investigation of the cyanohydrin equilibrium for the appropriate *p*-alkylbenzaldehyde should achieve this object. An equilibrium state is unaffected by polarisability effects and provides information regarding the permanent states of polarisation and hence of the relative stabilities of the molecules concerned. Lapworth has shown experimentally that, with substituents of the electron-release type, the stability of the cyanohydrin decreases with increasing electron-release. In the *p*-alkylbenzaldehyde the type of conjugation postulated by Baker and Nathan extends to the side-chain carbonyl group (III), whereas in the cyanohydrin (IV) it is restricted to the aromatic nucleus.

(III.)  (IV.)

It was therefore anticipated that the mesomeric electron-release by the *p*-alkyl substituent would stabilise the free aldehyde to a greater extent than it does the cyanohydrin. Moreover, the complete conjugation possible in (III) gave ground for hope that the effect of such mesomeric electron-release might predominate over any inductive effect and thus reveal an order *p*-$Me > Et > Pr^{\beta} > Bu^{\gamma} > H$ for stabilisation of the free aldehyde relative to its cyanohydrin.

The cyanohydrin equilibrium was studied quantitatively by Lapworth and Manske (J., 1928, 2533 *et seq.*) in constant boiling-point alcohol as solvent, and the scope of their investigation has now been extended to include the *p*-methyl-, -ethyl-, -*iso*propyl-, and -*tert.*-butyl-benzaldehydes at two temperatures. The values of the cyanohydrin dissociation constants, $K = k_2/k_1$ at 20° and 35°, all of which are the mean of several consistent determinations, are given in Table I, together with the corresponding values for the change in free energy $\Delta F = -RT \ln K$.* A new technique was necessary for the determinations at 35° (see p. 197).

TABLE I.

Equilibrium constants for the reaction (I) + HCN $\underset{k_2}{\overset{k_1}{\rightleftharpoons}}$ (II) *in constant-boiling alcohol at* 20° *and* 35°.

R.	10^3K, g.-mol.-l.$^{-1}$. 20°.	10^3K, g.-mol.-l.$^{-1}$. 35°.	$\Delta F \times 10^{-3}$, cals. 20°.	$\Delta F \times 10^{-3}$, cals. 35°.
H	*4·47 ± 0·12	8·80 ± 0·10	+31·5	+29·0
Me	*8·98 ± 0·13	20·32 ± 0·21	+27·5	+23·9
Et	8·18 ± 0·03	17·39 ± 0·09	+28·0	+24·8
Pr^{β}	8·04 ± 0·05	16·50 ± 0·06	+28·1	+25·1
Bu^{γ}	7·49 ± 0·17	15·04 ± 0·09	+28·5	+25·7

* These values are somewhat lower than those, 4·72 and 10·3 respectively, obtained by Lapworth and Manske (*loc. cit.*).

The order of the stabilities of the cyanohydrins, $H > \{Bu^{\gamma} > Pr^{\beta} > Et > Me\}$, relative to their respective aldehydes revealed by the values of K at both temperatures and by the corresponding well-spaced values of ΔF are completely in accord with theoretical anticipations and provide the first

* ΔF is calculated from this thermodynamic relationship and is thus the increase in free energy (at absolute zero) for the dissociation of the cyanohydrin into aldehyde and hydrogen cyanide. It should be noted that, since Lapworth and Manske used $\Delta F = RT \ln K$ in their evaluation of the free energy change, the signs of our values are the opposite of theirs.

conclusive evidence for the order of mesomeric electron-release Me > Et > Pr$^{\beta}$ > Bu$^{\gamma}$ required by Baker and Nathan's hypothesis.*

In order that a more complete theoretical discussion of the problem on the basis of relative energy levels might be possible it was necessary also to evaluate k_1 and k_2 individually. The determination of such kinetic data presented many difficulties from an experimental point of view. These were due mainly to three factors: (1) The great susceptibility of the reaction to fortuitous catalysts, and the consequent difficulty in obtaining reproducible results. (2) The ready oxidation of the aldehydes, which introduces small, but unknown, concentrations of acids. (3) The volatility and consequent loss of hydrogen cyanide during sampling. Disturbance due to (3) was reduced to a negligible minimum by devising a special apparatus (see p. 197) by means of which the reaction and sampling were carried out in an atmosphere of pure nitrogen under slight positive pressure. The problem of suitable catalysis presented by (1) and (2) was a two-fold one, *viz.*, to discover catalytic conditions which (*a*) gave reaction speeds convenient for measurement, and (*b*) were exactly reproducible. Even small concentrations of tri-*n*-propylamine (the catalyst in the equilibrium experiments) gave inconveniently large velocities: the very weak base acetamide was effective only in such concentrations as would seriously alter the nature of the medium. Pyridine was found to be adequate in small concentrations, but consistent results could not, at first, be obtained, probably owing to the formation of small, unknown amounts of pyridinium *p*-alkylbenzoate. It was shown, experimentally, that pyridinium benzoate has a smaller catalytic effect than pyridine itself. After a long systematic investigation of the effects of all the catalytic entities likely to be present under the reaction conditions, it was concluded that the catalyst used must contain sufficient base to swamp any catalytic effects of fortuitous alkali present (*e.g.*, from the glass vessels) and sufficient benzoate ions to render the small, unknown traces of acid produced by oxidation of the aldehyde negligible in comparison. The kinetic investigations were accordingly effected by using a mixture of 0·01M-pyridine + 0·01M-pyridinium benzoate as the standard catalyst. In several instances the reaction was allowed to proceed to equilibrium and the values of K so determined agreed with those obtained by using tri-*n*-propylamine as a catalyst.

The general reaction type is $A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} C$, and the authors are indebted to Dr. W. Wild of the Physical Chemistry Department of this University for the following derivation of the integrated kinetic expression for such a reversible addition.

If a = initial concentration of A (aldehyde), b = initial concentration of B (hydrogen cyanide), and x = concentration of C (cyanohydrin) at time t, then

$$dx/dt = k_1(a - x)(b - x) - k_2x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

At equilibrium $dx/dt = 0$ and $x = \Delta$, then, from (i)

$$k_2\Delta = k_1(a - \Delta)(b - \Delta)$$

or

$$k_2 = k_1(a - \Delta)(b - \Delta)/\Delta.$$

Substitution of this value in (i) gives

$$dx/dt = k_1(a - x)(b - x) - k_1(a - \Delta)(b - \Delta)x/\Delta$$

which on integration gives

$$k_1t = \frac{2{\cdot}303}{-\Delta} \log \frac{(x - \alpha)}{\alpha(x - \Delta)}, \text{ where } \alpha = ab/\Delta$$

i.e.,

$$\log_{10} \frac{x - \alpha}{x - \Delta} = \frac{k_1(\alpha - \Delta)t}{2{\cdot}303} - \log_{10} \frac{\Delta}{\alpha}.$$

The slope of the straight line obtained by plotting $f(x) = \log_{10}(x - \alpha)/(x - \Delta)$ against t is equal to $k_1(\alpha - \Delta)/(2{\cdot}303)$, whence k_1 was determined. k_2 was then found from

$$K = k_2/k_1, \text{ where } K = (a - \Delta)(b - \Delta)/\Delta.$$

The results agreed accurately with this straight-line relationship for a period of about 100 hours, corresponding to about 80% of the course of the reaction to the equilibrium position.

* The corresponding values of ΔH, calculated from the relationship $\Delta H = T_1T_2/(T_2 - T_1)R \ln K_2/K_1$, for the H, Me, Et, Pr$^{\beta}$, and Bu$^{\gamma}$ compounds are, respectively, 8089, 9752, 8999, 8585, and 8348 cals. This means that the changes in ΔF depend mainly on changes in $T\Delta S$ and not in ΔH, but it is generally recognised that the values of ΔF more truly reflect the energy changes in the molecule caused by substitution, and these values form a clear-cut series in harmony with the theoretical predictions.

The values of k_1 and k_2, each of which is the mean of at least two consistent determinations, at 20° ± 0·01° are given in Table II.

TABLE II.

Kinetic data for the reaction (I) + HCN $\underset{k_2}{\overset{k_1}{\rightleftharpoons}}$ (II) *in constant boiling-point alcohol at* 20° : 0·01M-*pyridine* + 0·01M-*pyridinium benzoate as catalyst.*

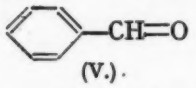
R =	H.	Me.	Et.	Prβ.	Buγ.
10^5k_1, sec.$^{-1}$ g.-mol.$^{-1}$l.	1·96	0·98	1·01	0·85	0·91
$10^{10}k_2$, sec.$^{-1}$	$0·87_8$	$0·88_3$	$0·82_5$	$0·68_3$	0·68

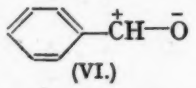
DISCUSSION.

The stabilisation of the aldehyde relative to its cyanohydrin will be effected by electron-release from the *p*-alkyl substituent by both the inductive (+ *I*) and the mesomeric (+ *M*) effect. The greater the total electron-release the greater is the relative stability of the free aldehyde. The experimental data clearly reveal an order of decreasing cyanohydrin stability H > Buγ > Prβ > Et > Me, proving an order of total electron-release, $(I_{Me} + M_{Me}) > (I_{Et} + M_{Et}) > (I_{Pr^\beta} + M_{Pr^\beta}) > (I_{Bu^\gamma} + M_{Bu^\gamma})$. The order of electron-release by the inductive effect is, however, known to be $I_{Bu^\gamma} > I_{Pr^\beta} > I_{Et} > I_{Me}$; hence the order of mesomeric electron-release must be $M_{Me} > M_{Et} > M_{Pr^\beta} > M_{Bu^\gamma}$, in agreement with the requirement of Baker and Nathan's hypothesis.

Correlated interpretation of both the equilibria and kinetic data is best effected by the method of relative energy levels applied to other side-chain reactions in previous papers in this series * (J., 1939, 1150; 1940, 692; *Trans. Faraday Soc.*, 1941, **37**, 632). It will be convenient to deal first with equilibria which involve only the energy levels of the ground states of the aldehyde and cyanohydrin molecules and then, by consideration of the energy levels of the activated transition complex, to extend the treatment to the interpretation of the velocity data.

(a) *Equilibria.*—In the ground state of benzaldehyde itself resonance will occur between structures of types (V), (VI) and (VII). Introduction of a *p*-alkyl substituent will lower the energy level (increase the stability), since structures of types (VIII) and (IX) can now also be included in the resonance hybrid.


(V.)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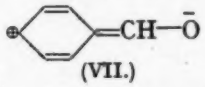
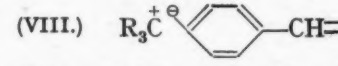
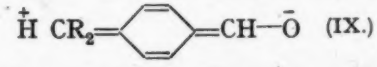

(VII.)

Of these, for reasons already given, (IX) is likely to be the more important, and the increased stabilisation will be greater the larger the number of C–H bonds which are directly conjugated with the aromatic

(VIII.) 


(IX.)

ring (*i.e.*, $CH_3 > MeCH_2 > Me_2CH > Me_3C$), being zero in the case of Buγ. The values assigned to the inductive and mesomeric effects of the various alkyl substituents and their total effect on the relative energy levels of the aldehyde are given in Table III. Because conjugation of the alkyl C–H bonds extends to the side-chain carbonyl group, the values of + *M* are greatly enhanced compared with those

* To avoid misconceptions it must be emphasised that the use of numerical values to represent the magnitudes of the inductive and tautomeric effects is merely a concise method of expressing changes in energy levels which result from substitution in the parent molecule, and so avoids (otherwise necessary) long verbal statements or graphical representation. The energy-level changes have a sonnd basis in physical theory, and the only arbitrary factors in the numerical values are the (unknown) units in which they are measured and their *absolute* magnitudes. The *differences* in magnitudes thus disclosed between various groups are always strictly in at least qualitative agreement with the established relative magnitudes of the inductive and tautomeric effects. The statement that " the stability of benzaldehyde is increased, *i.e.*, its energy level is lowered, by both the inductive and the tautomeric electron-release of a *p*-methyl substituent " is concisely represented by the three sets of figures in the first line of the left-hand column of Table III. " The lowering of the energy level by similar introduction of a *p*-ethyl group will be greater than that of methyl by virtue of its inductive effect, but less than that of methyl by virtue of its tautomeric effect " is again concisely represented in the second line of the same column in Table III, which assigns a larger value (25) to the inductive effect of ethyl than that (10) of methyl, and a smaller value (80 instead of 120, since two C–H bonds instead of three are conjugated with the rest of the molecule) to its tautomeric effect. The figures under " $_{\Delta}E_{\phi}$," for example, then indicate concisely that the energy levels of benzaldehyde and its *p*-alkyl derivatives are in the order H > Buγ > Prβ > Et > Me. The graphical method of representation was used in the first application of this treatment (Baker, J., 1939, 1150) and the adoption of the tabular system used in Table III is merely to avoid the expense of blocks necessitated by the former method.

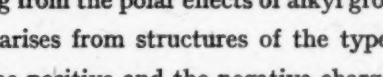
used in the interpretation of the dipole-moment data for *p*-alkylbenzenes in the vapour phase (Baker, J., 1939, 1150) although, of course, the relative magnitudes are still in the ratio Me : Et : Pr^{β} : Bu^{γ} = 3 : 2 : 1 : 0. The rather large differences in the magnitudes previously assigned to the inductive effects have, however, been reduced for the following reason. The dipole-moment data refer not so much to energy levels as to the charge separation arising from the polar effects of alkyl groups. In the mesomeric component of such electron-release, since it arises from structures of the type  in the resonance hybrid, the distance between the positive and the negative charge is approximately constant for all alkyl substituents. The polar effect of the alkyl group due to the operation of its inductive effect gives rise to a positive charge which will be distributed in the group CR_3. As the constitution of this group alters from CH_3 to $C(CH_3)_3$ the average location of this positive charge will be situated at an increasing distance from the aromatic nucleus. The arbitrary values assigned to the inductive component on the basis of dipole moments will thus be a measure of the product of charge × effective distance. Since the distance increases in passing from toluene to *tert.*-butylbenzene, the relative magnitudes assigned to the inductive effects of the various alkyl substituents will tend to be too large and the discrepancy will increase as the complexity of the alkyl group increases. Smaller differences between the various values of the $+I$ components have therefore been assigned in Table III, especially in the higher alkyl groups. The established sequence of magnitude Me < Et < Pr^{β} < Bu^{γ} is, of course, maintained.

TABLE III.

Relative energy levels in the ground and the activated states of *p*-$C_6H_4R{\cdot}CHO$ *and* *p*-$C_6H_4R{\cdot}CH(OH){\cdot}CN$.

(Standard energy level, R = H.)

	Reductions in energy levels in the ground state of aldehyde.			Reductions in energy level in the activated state.			Reductions in energy levels in the ground state of cyanohydrin.		
R.	$+I$.	$+M$.	${}_{A}E_{g}$.†	$+I$.	$+M$.	E_{a}.†	$+I$.	$+M$.	${}_{O}E_{g}$.†
Me	10	120	130	4	100	104	6	99	105
Et	25	80	105	14	67	81	18	66	84
Pr^{β}	39	40	79	16	33	49	26	33	59
Bu^{γ}	50	0	50	22	0	22	32	0	32

† Positive values for ${}_{A}E_{g}$, etc., mean a positive *reduction* in the energy level, *i.e.*, a lower energy level.

In the ground state of the cyanohydrin, formal conjugation does not extend into the side chain, and hence electron-release by the mesomeric mechanism will be smaller than in the parent aldehyde. A similar, but smaller, reduction has been made in the values assigned to the inductive effects in Table III because of the smaller electron-attraction of the side chain −CH(OH)·CN than of −CH:O.

It will be seen that the relative energy levels in the ground states of the free aldehyde (${}_{A}E_{g}$) and its cyanohydrin (${}_{O}E_{g}$) are both in agreement with an order of stabilisation H < Bu^{γ} < Pr^{β} < Et < Me, but that the stabilising effect of any particular alkyl substituent is greater in the free aldehyde than in its cyanohydrin (${}_{A}E_{g} > {}_{O}E_{g}$). The differences ${}_{A}E_{g} - {}_{O}E_{g}$ * are a measure of the stability of the aldehyde relative to its cyanohydrin, *i.e.*, of the relative values of K : the greater the difference the larger the value of the dissociation constant K. These differences are Me 25, Et 21, Pr^{β} 20, Bu^{γ} 18, in harmony with the observed sequence for K, *viz.*, H < Bu^{γ} < Pr^{β} < Et < Me.

The view that the values of K are determined largely by the relatively greater stabilising effects of the alkyl group conjugated with carbonyl in the free aldehydes receives striking confirmation from the results of Lapworth and Manske (J., 1930, 1978) for phenyl alkyl ketones Ph·COR, which were obtained under exactly the same experimental conditions as our own. They are as follows :

R =	H.	Me.	Et.	Pr^{β}.	Bu^{γ}.
$10^{3}K$	47	1300	600	250	90
$\Delta F \times 10^{-3}$ ‡	+31	−2	+3	+8	+14

‡ The signs of Lapworth and Manske's values for ΔF have been reversed to make them correspond with our values based on $\Delta F = -RT \ln K$ (see footnote, p. 192).

The large decrease in stability of the cyanohydrin in passing from benzaldehyde to acetophenone evidently arises from the increased stabilisation of the free carbonyl compound due to structures of the type $Ph{\cdot}\overset{\bar{O}}{C}{=}\overset{+}{C}H_2$, and the order of cyanohydrin stability (R =) H > Bu^{γ} > Pr^{β} > Et > Me is that anticipated

* See footnote on p. 196.

on the basis of the number of C–H bonds in the alkyl group R which are conjugated with C:O. When R = Ph the possibilities of conjugation are greatly enhanced, and this should cause much greater stabilisation of the ketone relative to its cyanohydrin. This accords with the fact that Lapworth (J., 1928, 2548) found no measurable formation of the cyanohydrin with benzophenone, *i.e.*, K approaches infinity. This large effect of phenyl only operates when the group is directly conjugated with the carbonyl group, since the equilibrium constants for the cyanohydrin formation of $CH_3 \cdot CO \cdot CH_2Ph$ ($10^3K = 21{\cdot}5$, $10^{-2}\Delta F = +22$) and $CH_3 \cdot CO \cdot CH_2Me$ ($10^3K = 26{\cdot}5$, $10^{-2}\Delta F = +21$) (Lapworth and Manske, *loc. cit.*) are closely comparable in magnitude. In both these ketones there are five C–H bonds conjugated with the C:O group.

(b) *Kinetic Data.*—The common activated transition complex for both forward and back reactions will be a resonance hybrid symmetrically related to structures of types (X) and (XI). In this complex,

electron-release from the *p*-alkyl substituent by the tautomeric mechanism would presumably be smaller than in the ground state of the free aldehyde owing to the opposing electron displacements initiated by the negative charge in the side chain. A proportionately greater diminution should occur in the inductive component. Account is taken of these factors in the values assigned in Table III.

The differences ${}_A E_g - E_a$ (δE_{k_1}) * are a qualitative measure of the energies of activation for the forward reaction. They are:

R =	Me.	Et.	Pr$^\beta$.	Bu$^\gamma$.
δE_{k_1}	26	24	30	28

in agreement with the sequence observed for k_1, *viz.*, H > Et > Me > Bu$^\gamma$ > Pr$^\beta$. Similarly, $\delta E_{k_2} = {}_O E_g - E_a$, a measure of the energies of activation for the back reaction, has the values Me 1, Et 3, Pr$^\beta$ 10, Bu$^\gamma$ 10, in harmony with the observed velocity sequence for k_2, *viz.*, H ≃ Me > Et > Pr$^\beta$ ≃ Bu$^\gamma$.

It is thus apparent that not only the regular sequence observed in the equilibria but also the "muddled" sequences of the velocity data receive a complete and consistent explanation on the basis of the same sets of relative energy levels derived from the theoretical concepts of the polar effects of alkyl groups recently developed in this series of papers. In conclusion, it may be noted that a close resemblance can be traced between the cyanohydrin reaction and the electrolytic reduction of the aldehydes at a dropping-mercury cathode (Baker, Davies, and Hemming, J., 1940, 692), and the complex results revealed in the latter investigation also receive a satisfactory explanation on the basis of very closely similar sets of values for the energy levels of ground and activated states (cf. Hemming, Thesis, University of Leeds, 1940).

Experimental.

Preparation of Materials.—The *p*-alkylbenzaldehydes were prepared and purified by the methods given by Baker, Davies, and Hemming (*loc. cit.*). In every case purification involved conversion first into the bisulphite compound and then into the semicarbazone. Regeneration of the aldehyde from the purified semicarbazone was effected by steam-distillation with oxalic acid in an atmosphere of carbon dioxide, followed by repeated fractionation under reduced pressure in a current of nitrogen. All samples were stored in the dark under nitrogen and were redistilled into the weight pipette with the same precautions immediately before use. The samples used had the following b. p.'s: benzaldehyde, 73°/21 mm.; *p*-methyl-, 98°/24 mm.; *p*-ethyl-, 64·2°/1·2 mm.; *p-iso*propyl-, 120°/23 mm.; *p-tert.*-butyl-benzaldehyde, 80°/0·9 mm.

Liquid hydrogen cyanide was prepared as described in "Organic Syntheses," 1927, VII, 50, and was refractionated from phosphoric oxide in an all-glass apparatus. The standard solution was prepared by dissolving 16 c.c. of the liquid in 400 c.c. of constant boiling-point alcohol, and was stored in well-stoppered brown bottles sealed with paraffin wax. Its concentration (approximately 10 m.-mol./10 c.c.) remained unchanged over long periods.

Aqueous alcohol (64 O.P. = 93·5% by vol.) was refluxed with 2% of oxalic acid, fractionated through a Widmer column, refluxed with 5% by weight of sodium hydroxide, again distilled through a column, and finally repeatedly fractionated, the portion of constant b. p. (78·5°) being stored for use. All-glass apparatus was used throughout.

Calibration of Apparatus.—All flasks and pipettes were carefully calibrated by weight and checked against

* If x and y are, respectively, the energy levels of the ground and activated states in the unsubstituted (reference) compounds, then in, *e.g.*, the methyl compounds the energy level in the ground state is $(x - 130)$ and, in the activated state, $(y - 104)$. The activation energy for the unsubstituted compound is $y - x$, and for the methyl compound, $(y - 104) - (x - 130) = y - x + 26$ (${}_A E_g - E_a$). The values of δE_k are thus measures of the *increases* in the potential energies of activation over the standard reference values for the unsubstituted compound.

each other, those used for alcoholic solutions being calibrated with this solvent. For titrations an N.P.L. standard semi-micro burette, reading to 0·01 c.c., was employed.

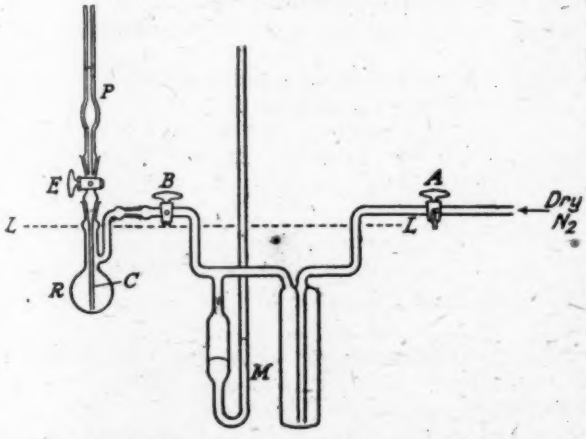
Determination of Equilibrium Constants.—At 20° the technique of Lapworth and Manske (*loc. cit.*), slightly modified and standardised to minimise loss due to the volatility of hydrogen cyanide, was employed. In preparation of the reaction mixture, exposure of the aldehyde to the air was reduced to a minimum and no appreciable oxidation was possible with the technique used. The titrations on the hydrogen cyanide solution (blank) always agreed to ± 0·02 c.c. and the consistency of the various determinations of K is illustrated by the values obtained with benzaldehyde: 10^3K = 4·57, 4·51, 4·25, 4·39, 4·27, 4·56, 4·44, 4·70: mean 4·47 ± 0·12. The value 4·57 was obtained from one velocity determination which was left until equilibrium was attained. The mean deviations from the mean are recorded in each case in Table I.

At 35° this technique was unsatisfactory, presumably owing to the greater and irregular losses of hydrogen cyanide during sampling. The following sealed-bulb technique was therefore developed, and is regarded as a marked improvement on that of Lapworth and Manske.

A series of bulb tubes (see Fig. 1) were made from 4″ × ½″ test-tubes such that (1) the constricted portion was wide enough for insertion of the stem of a 2-c.c. pipette; (2) they contained 10 c.c. when filled to a mark low down on the constricted portion, and (3) the bulbs were of such thickness that they would withstand the slight pressure developed in the thermostat but could easily be broken under the silver nitrate solution after equilibration was complete. The bulbs, cleaned with the pure solvent, were calibrated in the thermostat with 10 c.c. of pure solvent at 35°, and a mark made on the constricted portion. The appropriate quantity of aldehyde was delivered from a weight pipette, with the usual precautions, into about 3 c.c. of the solvent (containing the requisite amount of tri-*n*-propylamine in solution), the space above this solvent having previously been filled with nitrogen. Any trace of aldehyde in the constriction was immediately washed down with more solvent. 2 C.c. of the standard hydrogen cyanide solution were added and the total volume was adjusted to the 10 c.c. mark in the thermostat. The tube was kept closed with a well-fitting rubber stopper during these operations. The bulb was then cooled in a good freezing mixture, and sealed near the top of the constricted portion. After immersion in the thermostat for 24 hours the outside was well washed with distilled water at 35°, and the bulb broken under an appropriate volume of 0·05N-silver nitrate and nitric acid, also at 35°. The excess of silver nitrate, arranged to be about 5 c.c., was determined with ammonium thiocyanate in the usual manner. The consistency of the results is illustrated by details (Table IV) of the determinations with *p-tert.*-butylbenzaldehyde.

FIG. 1.

FIG. 2.



Velocity Determinations.—The preliminary work to determine suitable experimental conditions and to evaluate the effects of possible errors has been summarised (p. 193). Full details are given in the thesis referred to on p. 196.

The all-glass apparatus used for the kinetic measurements is shown in Fig. 2, devised so that the sample could be transferred from the reaction flask R to the calibrated 2-c.c. pipette P by pressure of nitrogen. The drawn-out end of P was ground into the cone above the tap E, the dead space above this tap being as smallas possible. All ground glass joints in the apparatus were standard and interchangeable. The whole apparatus could be immersed in the thermostat to the line LL. Immediately before each determination the whole apparatus

TABLE IV.

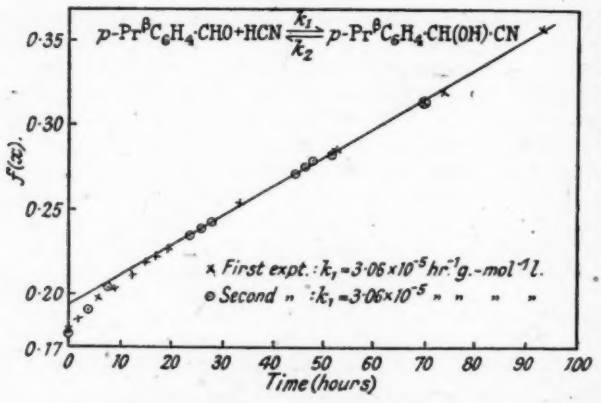
Vol. of HCN solution = 2 c.c. Total vol. = 10 c.c. Temp. 35° ± 0·05°.

No.	Wt. of aldehyde, g.	0·05N-$AgNO_3$ used, c.c.	0·05N-NH_4NCS for excess, c.c.	0·05N-$AgNO_3$ for free HCN, c.c.	N_A.	N_{HCN}.	$N_{Cyan.}$	$N_{R\cdot CHO}$.	10^3K, g.-mol.$^{-1}$.l.
1	0·4184	10	4·69	5·31	12·905	1·328	8·220	4·685	15·14
2	0·4468	10	5·37$_5$	4·62$_5$	13·780	1·156	8·374	5·406	14·93
3	0·4518	10	5·40$_5$	4·59$_5$	13·935	1·149	8·399	5·536	15·14
4	0·4470	10	5·35	4·65	13·785	1·163	8·387	5·395	14·96
	Blank	40 (1—3)	1·88	38·12	—	9·530	—	—	—
		40 (4)	1·80	38·20	—	9·550	—	—	—

N_A is the initial concentration of aldehyde, and N_{HCN}, $N_{Cyan.}$, and $N_{R\cdot CHO}$ are the equilibrium concentrations of free HCN, cyanohydrin, and free aldehyde, respectively, in m.-mols./50 c.c.

was swept out with a stream of pure, dry, oxygen-free nitrogen. About 10 mg.-mols. of the aldehyde were transferred from a weight-pipette (with the usual precautions) into 20 c.c. of the solvent alcohol, 0·02M with respect to both pyridine and pyridinium benzoate, in a 25-c.c. calibrated flask, and adjustment to the mark was made with more solvent catalyst after thermal equilibrium had been attained in the thermostat. A solution containing 20 c.c. of the stock alcoholic solution of hydrogen cyanide in 50 c.c. of the pure solvent alcohol was similarly prepared. The concentration of the latter solution was determined by withdrawing 5 c.c. and delivering it under the surface of 40 c.c. of 0·05N-silver nitrate, the excess of which was determined in the usual manner. 20 C.c. of the aldehyde solution were pipetted into the reaction flask *R* (of about 50 c.c. capacity) and, at zero time, 20 c.c. of the hydrogen cyanide solution were added, thus diluting the catalyst concentration to 0·01M. The tap-head *E* with its pipette were immediately inserted, and the reaction flask was attached to the rest of the apparatus. With taps *E* and *B* closed, the nitrogen stream (previously by-passed into the air through the three-way tap *A*) was passed into the apparatus until a pressure of approximately 50 mm. was registered on the manometer *M*. By manipulation of taps *E* and *B*, a sample of the reaction mixture was gently forced into *P*, and the free hydrogen cyanide in this 2-c.c. sample was determined in the usual way. The small amount of liquid remaining in the cone above *E* was dried out with filter-paper, and the column of liquid in the tube *C* was allowed to fall back into the flask by a momentary release of the nitrogen pressure in the apparatus. Between sampling, the cone above *E* was closed with a glass stopper.

FIG. 3.



The reaction was usually followed for about 100 hours, and the plot of about 15 values of $\log_{10}(x-\alpha)/(x-\Delta)$ against t always gave a good straight line from the slope of which k_1 was determined as indicated on p. 193. At least two consistent values of k_1 were obtained with each aldehyde. The reproducibility of the results is illustrated in Fig. 3, which gives the plot of f(x) against t for *p-iso*propylbenzaldehyde, using the actual working units, *viz.*, mg.-mols./40 c.c. and hours.

It will be noticed that a slight divergence from the straight line occurs during the first 10% of the reaction. It was proved that such divergences could not be accounted for by changes in either the value of K or of the initial hydrogen cyanide concentration much greater than the probable experimental errors. Since, in isolated examples, strict adherence to the straight-line relationship was observed right from the start of the reaction, these small initial disturbances are regarded as due to purely fortuitous circumstances.

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34. *The Triterpene Group. Part IX. The Constitution of Breïn and Maniladiol.*

By ISOBEL M. MORICE and JAMES C. E. SIMPSON.

It is shown that a close structural relationship probably obtains between breïn and maniladiol, the two principal diols of *Manila elemi* resin. Both isomerides are singly unsaturated, pentacyclic, di-secondary glycols; they probably differ in the location of their ethenoid linkages, but it is possible that their hydroxylated positions are identical. There is no close association either between the hydroxyl groups themselves, or between these and the double bond, in either diol. Efforts to establish an experimental relationship between the diols and either of the amyrins have been unsuccessful. The *methyl ethers* of α- and β-amyrin have been prepared, and also β-*amyrin p-toluenesulphonate*; the latter compound is unexpectedly stable in acid media.

IN previous papers (Morice and Simpson, J., 1940, 795; 1941, 181) we have shown that *Manila elemi* resin is a remarkably prolific source of triterpene alcohols, the two principal diols being the isomeric substances breïn and maniladiol. We now describe experiments which we have recently carried out with a view to the elucidation of the structure of these two diols.

Breïn.—Vesterberg (*Ber.*, 1906, **39**, 2467) suggested on biogenetic grounds that breïn is probably a hydroxyamyrin. In the work here described we have found that the diol is pentacyclic, that it resembles

α- rather than β-amyrin, that both hydroxyls are secondary, and that only one of them can be in ring A; we have, however, been unable to convert breïn into any known derivative of the amyrins.

The similarity between breïn and α-amyrin is indicated by the reluctance of the diacetate to react with perbenzoic acid. In one experiment, in which a 0·25N-solution of the acid in chloroform was used, only 0·03 atom of oxygen was absorbed during 14 days, and the diacetate was recovered in practically quantitative yield. In other experiments, small but appreciable amounts of oxygen were absorbed, but the only material recovered was the rather impure diacetate. The diol, however, is undoubtedly unsaturated (tetranitromethane), so the double bond is evidently of the extremely inert type present in α-amyrin, in contrast to the comparatively reactive unsaturated position characteristic of β-amyrin (Ruzicka, Silbermann, and Furter, *Helv. Chim. Acta*, 1932, **15**, 482). Furthermore, treatment of breïn dibenzoate with sulphur in boiling benzyl acetate leads to general decomposition of part of the ester, the remainder being recoverable, but in an impure condition; this behaviour would be unexpected if the diol were a β-amyrin derivative, but is not inconsistent with the view that the double bond may occupy the position characteristic of α-amyrin, because the methyl ester of acetyl-β-boswellic acid, which belongs to the α-amyrin group (Ruzicka and Wirz, *Helv. Chim. Acta*, 1939, **22**, 948), is largely unattacked under these conditions (Simpson and Williams, J., 1938, 1712).

Oxidation of breïn diacetate with chromic anhydride gives a good yield of a new *diacetate*, $C_{34}H_{52}O_5$, which shows the absorption spectrum of an αβ-unsaturated ketone, and gives no colour with tetranitromethane. It follows that breïn contains only a single ethenoid linkage (which must be of the type $>C{=}CH{-}CH_2-$), and the diol is therefore pentacyclic. Alkaline hydrolysis of the keto-diacetate yields the corresponding keto-diol, *breienediolone*, m. p. 249°.

The secondary nature of both hydroxyl groups in breïn is suggested by the fact that we have been unable to obtain any evidence of selective hydrolysis of breïn diacetate, and by the extremely smooth oxidation of the diol with chromic anhydride at room temperature to the corresponding dicarbonyl compound. This substance, which we now name breienedione, was originally obtained in very poor yield by Rollett (*Monatsh.*, 1929, **53—54**, 231) by oxidation with the same reagent on the water-bath. This author, on the basis of his analytical data and of the formation from the compound of only a monoxime, was unable to decide whether one or both of the hydroxyl groups had undergone oxidation. We have confirmed the formation of the monoxime, but we regard the compound as a diketone in view of its reduction by aluminium *iso*propoxide to a mixture of two keto-alcohols, *breieneonol*-A and -B, each of which has been characterised as a monohydric alcohol by the preparation of the corresponding *acetate*. These keto-alcohols are probably epimeric, and may be considered to result from the reduction of the C_2-carbonyl of breienedione (this also is presumably the carbonyl group of the diketone which reacts with hydroxylamine). Reduction of the C_2-carbonyl group by aluminium *iso*propoxide has already been observed in the case of nor-β-boswellanedione (Simpson and Williams, *loc. cit.*). Breienedione exhibits weak selective absorption in the ultra-violet which is indicative of isolated carbonyl groups; these, therefore, cannot be conjugated either with each other or with the double bond.

The absence of an aldehydic carbonyl in breienedione is confirmed by the stability of the compound towards chromic anhydride, by which it is attacked extremely slowly at temperatures below 55—60°. At about 65° the diketone yields a mixture of acid and neutral resins, the latter predominating. No crystalline substance could be obtained from the acid fraction, but the neutral material on treatment with semicarbazide furnished a yellow, crystalline *semicarbazone*, m. p. 194°. The formula of this substance suggested by analysis is $C_{31}H_{49}O_2N_3$, but the amount available was too small to permit further investigation.

The foregoing evidence clearly indicates that breïn cannot be an α-glycol. A primary-secondary β-glycol grouping of the hederagenin type is similarly excluded, and in agreement with this conclusion we find that the diol does not yield an acetonyl derivative in presence of hydrochloric acid. It may be noted in passing that condensation with acetone is not rigidly indicative of the presence of the system $CH_2(OH)\cdot\overset{|}{C}\cdot CH(OH)-$ in a triterpene diol, because, although hederagenin and bassic acid both form acetonyl derivatives (Jacobs, *J. Biol. Chem.*, 1925, **63**, 631; Heywood, Kon, and Ware, J., 1939, 1124), soyasapogenol-B, in which the same system is present (Tsuda and Kitagawa, *Ber.*, 1938, **71**, 790, 1604), does not do so. The possibility that breïn might be a disecondary β-glycol can also be eliminated for the reason that breienedione would then be a β-diketone, a formulation which is inconsistent with the reluctance of the compound to undergo further oxidation. It therefore follows that the second hydroxyl group of breïn cannot be in ring A.

In attempting to relate breïn to either α- or β-amyrin, we at first sought to effect the removal of hydroxyl groups from the diol by means of phosphorus pentachloride, the dehydrating action of which

upon triterpene alcohols has been frequently observed (compare Vesterberg, *Ber.*, 1887, **20**, 1247; Nojd, *Arch. Pharm.*, 1927, **265**, 381) In the case of brein, however, uncrystallisable resins resulted, and milder conditions were apparently required. We considered that *p*-toluenesulphonyl chloride might fill this need, because this reagent forms reactive esters with cholesterol and other sterols (Stoll, *Z. physiol. Chem.*, 1932, **207**, 147), which readily undergo double decomposition in alcoholic solution. Although the reactivity of these steroid tosylates is evidently dependent on the proximity of the 5 : 6 double bond to the tosyl group, it nevertheless seemed possible that the more readily dehydrated triterpene alcohols might undergo spontaneous dehydration, or at least yield reactive tosylates which could be broken down to the sulphonic acid and unsaturated hydrocarbons. To test this hypothesis, the tosylation of β-amyrin was carried out, with the result that *β-amyrin p-toluenesulphonate* was isolated in high yield. This ester, however, proved to be unexpectedly stable, and highly resistant to fission in acid media; experiments in this direction were therefore discontinued.

The reduction of breienedione by the Clemmensen method furnished a poor yield of a *hydrocarbon*, m. p. 143°, analysis of which suggested the molecular formula $C_{30}H_{48}$ rather than the expected composition $C_{30}H_{50}$. The physical constants of the compound, however, are not in agreement with those of any of the known amyrilenes or amyrenes.

As an alternative means of establishing a relationship between brein and the amyrins, we considered that methylation of breieneonol-A, followed by Clemmensen reduction, might give rise to the methyl ether of α- or β-amyrin. These *ethers*, hitherto unknown, were accordingly prepared from the corresponding alcohols by means of emulsified potassium and methyl iodide; the alkylations were extremely sluggish in comparison with those of ergosterol derivatives by the same method (Heilbron and Simpson, J., 1932, 268). Each ether was stable towards the Clemmensen reagent under the conditions employed in the preparation of the hydrocarbon from breienedione. When, however, the methylation of breieneonol-A was attempted *via* the potassium derivative, decomposition rapidly set in with production of a resin, and further search for the correct methylation conditions was prevented by lack of material.

Finally, the reduction of breienedione with hydrazine and sodium ethoxide was investigated; here again, however, resinification occurred, and no serviceable product could be isolated.

Maniladiol.—The fact that brein and maniladiol occur in very close association in *Manila elemi* resin (Morice and Simpson, *locc. cit.*) is suggestive of a correspondingly intimate chemical relationship between them. The physical constants of corresponding derivatives of the two isomerides are, indeed, strikingly similar in many instances, as may be seen from the accompanying Table.

	Maniladiol.		Brein.	
	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.
Diol	220—221°	+68°	221—222°	+63·5°
Diacetate	193—194	+80	197—198	+70
Diformate	191—192	+84	220—221	+67
Dibenzoate	233—234	+63·5	209—210	+58
Diketone	209—210	+48	159—160	+66
Oxime of diketone	272—274	—	250—252	—
Keto-diacetate	224—225	+93	222—223	+90
Keto-diol	240—241	+88	247—249	+82

The diols, however, appear to differ in the reactivity, and therefore probably also in the location, of their unsaturated centres. For instance in a perbenzoic acid titration, conditions being used under which brein diacetate absorbed only 0·03 atom of oxygen, maniladiol diacetate reacted with 0·53 atom of oxygen; the product was a mixture which still gave a positive tetranitromethane reaction, although the melting point was depressed by the parent diacetate. That maniladiol contains only one unsaturated position, and is therefore pentacyclic, follows from the ready oxidation of the diacetate to a *compound*, $C_{34}H_{52}O_5$, which shows the absorption spectrum of an αβ-unsaturated ketone and gives a negative tetranitromethane reaction. As in the case of the brein derivative, this new diacetate easily yields the related *keto-diol* on hydrolysis.

Oxidation of the free diol at room temperature proceeds smoothly, as with brein, to the corresponding diketone, *maniladione*, the absorption spectrum of which indicates the absence of conjugation, and closely resembles that of breienedione. Maniladione forms a *monoxime*, fails to react with Schiff's reagent, and is stable to chromic anhydride below 50°. At 63° it yields on oxidation an *acid* of probable formula $C_{30}H_{46}O_5$, presumably formed by fission of ring A at C_2–C_3, together with a yellow neutral *substance*, $C_{30}H_{44}O_3$. The colour of the latter persists after treatment with charcoal and activated alumina, and we therefore regard it as characteristic of the compound.

For the reasons given in the section dealing with brein, it follows from the above facts that manila-

diol is a disecondary glycol in which ring A can contain only one hydroxyl group (presumably attached to C_2). No acetonyl derivative could be obtained from maniladiol.

Unsuccessful attempts were made to reduce maniladione to a hydrocarbon. With hydrazine and sodium ethoxide a low yield of a crystalline *substance* was obtained, but the analytical values were approximately those of a monohydric alcohol; lack of material prevented further characterisation of the product. The Clemmensen procedure, as with breienedione, furnished a mixture, but in this case no oxygen-free substance could be isolated.

Although the war has prevented the completion of this investigation, the evidence here recorded is indicative of a close structural relationship between breïn and maniladiol, and is consistent with the provisional hypothesis that the two diols differ in the location of their unsaturated centres, although it is possible that their hydroxylated positions may be identical.

We are indebted to Dr. R. A. Morton for the spectrographic data.

Experimental.

(Melting points are uncorrected, and specific rotations were measured in chloroform solution.)

Oxidation of Breïn with Chromic Anhydride.—(*A*) *Breienedione.* A solution of chromic anhydride (2 g.) in water (5 c.c.) and glacial acetic acid (195 c.c.) was added with stirring to a solution of breïn (4 g.) in acetic acid (1 l. of 95%) at room temperature during 3 hours. After a further 3 hours the solution was diluted with water (3 vols.), and the precipitate collected and washed. It was then taken up in ether, and the solution, after being washed with aqueous sodium hydroxide (no acid fraction was present) and with water, was dried and evaporated. Two crystallisations of the residue from aqueous methanol yielded the pure diketone (2·7 g.), which formed both octahedra, m. p. 150—151°, $[\alpha]_D^{16°} + 67°$ ($l = 1$, $c = 2·81$), and long prisms, m. p. 159—160°, $[\alpha]_D^{17°} + 66°$ ($l = 1$, $c = 2·435$), either form being obtainable from a solution of the other by nucleation (Found: C, 82·0, 82·1; H, 10·5, 10·5. Calc. for $C_{30}H_{48}O_2$: C, 81·7; H, 11·0%. Calc. for $C_{30}H_{46}O_2$: C, 82·1; H, 10·6%). *Light absorption in alcohol:* Maximum at 2950 A., $\log \varepsilon = 1·833$.

The monoxime, prepared in aqueous-alcoholic solution, separated from methanol in shining leaflets, m. p. 250—252° (decomp.) (Found: C, 79·2; H, 10·4; N, 3·6. Calc. for $C_{30}H_{47}O_2N$: C, 79·4; H, 10·5; N, 3·1%).

(*B*) A solution of the diol (0·5 g.) in acetic acid (50 c.c. of 95%) was treated with a solution of chromic anhydride (0·5 g.) in water (5 c.c.) and acetic acid (45 c.c.), added with stirring at 63° during 1 hour. After a further hour, most of the solvent was removed under reduced pressure, water added to the residue, and the precipitate collected and washed. It was then dissolved in ether and separated into acid and neutral fractions with 2% aqueous sodium hydroxide.

The acid fraction, obtained by acidification of the alkaline washings with dilute hydrochloric acid and extraction with ether, was a resin which could not be crystallised. It was methylated with ethereal diazomethane, but again no crystalline material could be obtained.

The ethereal solution containing the neutral material, after being washed, dried, and evaporated, yielded a yellow resin (0·36 g.). After unsuccessful attempts at crystallisation, this material was refluxed with semicarbazide hydrochloride (0·4 g.) and sodium acetate (0·6 g.) in aqueous alcohol (45 c.c.) for 4 hours; water was then added, and the product extracted with ether. The residue from the washed and dried extract crystallised from benzene–ligroin, and after several crystallisations the *semicarbazone* separated in small yellow prisms, m. p. 193—194° (decomp.), $[\alpha]_D^{17°} + 111°$ ($l = 1$, $c = 0·415$) (Found: C, 72·0; H, 9·5; N, 8·6. $C_{31}H_{49}O_2N_3$ requires C, 72·7% H, 9·7; N, 8·2%).

The same compound was also obtained by an analogous oxidation of breienedione.

Reduction of Breienedione.—(A) *By the Clemmensen method.* A solution of the diketone (0·6 g.) in glacial acetic acid (52 c.c.) was refluxed for 10 hours with amalgamated zinc dust (22 g.) and concentrated hydrochloric acid (22 c.c.). Water was then added, and the precipitated organic material extracted with ether. The extract was washed with water, aqueous sodium carbonate, and again with water, dried and evaporated. The residue crystallised from acetone, and after six crystallisations from this solvent, which involved heavy losses of material, shining leaflets (30 mg.) of a *hydrocarbon* were obtained, m. p. (constant) 142—143°, $[\alpha]_D^{13°} + 40°$ ($l = 1$, $c = 1·035$). The addition of tetranitromethane to a solution of the hydrocarbon in chloroform produced a yellow colour, and in the Liebermann–Burchard test the colour changed from pink through orange to brown (Found: C, 88·4; H, 11·85. $C_{30}H_{48}$ requires C, 88·15; H, 11·85%. $C_{30}H_{50}$ requires C, 87·7; H, 12·3%).

The crystalline material in the mother-liquors was a mixture; one fraction was isolated which melted constantly at 129—131°, but analysis showed this to be a mixture of hydrocarbon and oxygenated material (Found: C, 86·0, 86·2; H, 11·9, 11·8%).

(B) *With hydrazine and sodium ethoxide.* The reduction was carried out as described for maniladione (*q.v.*). No crystalline product could be obtained from the resultant resin, either directly or by adsorption on activated alumina.

(C) *With aluminium* iso*propoxide.* A solution of breienedione (2·6 g., dried at 130° in a vacuum) in *iso*propyl alcohol (220 c.c.) was refluxed for 3½ hours with aluminium *iso*propoxide (11 g.). Water and dilute sulphuric acid were added, and the precipitated material extracted with ether. The residue from the washed,

dried, and evaporated extract could not be satisfactorily purified by crystallisation; it was therefore dissolved in benzene, and the solution was drawn through a column (1·4 × 67 cm.) of activated alumina (100 g.). The bulk of the material was only weakly adsorbed, and on recrystallisation from methanol yielded lustrous plates (0·48 g.) of *breieneonol*-A, m. p. 208—209°, $[\alpha]_D^{17°}$ + 37° (l = 1, c = 2·385) (Found: C, 81·7; H, 11·0. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). The keto-alcohol was characterised by the preparation of the *acetate* (pyridine and acetic anhydride); this separated from aqueous methanol in clusters of prisms, m. p. 133—135°, $[\alpha]_D^{22°}$ − 13° (l = 1, c = 0·555) (Found: C, 79·4; H, 10·35. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%).

The crude reduction product of breienedione contained a small amount of material which was strongly adsorbed on alumina. On recrystallisation of this from methanol, prisms of *breieneonol*-B were obtained (0·16 g.), m. p. 226—227°, $[\alpha]_D^{18°}$ + 48° (l = 1, c = 2·65) (Found: C, 81·9; H, 11·1. $C_{30}H_{48}O_2$ requires C, 81·75; H, 11·0%). The *acetate* formed prismatic needles from methanol, m. p. 212—213°, $[\alpha]_D^{22°}$ + 46° (l = 1, c = 1·47) (Found: C, 79·5; H, 10·2. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·45%).

Oxidation of Breïn Diacetate.—A solution of chromic anhydride (0·15 g.) in water (1 c.c.) and acetic acid (6·5 c.c.) was added during ½ hour at 95° to a solution of breïn diacetate (0·3 g.) in acetic acid (15 c.c. of 95%) with continuous stirring. After a further ½ hour, the solution was diluted with water (3 vols.), and the resultant precipitate collected, washed, and dissolved in ether. The solution was washed with aqueous sodium hydroxide (no acid fraction was present), and again with water. After drying and evaporation, a crystalline residue was obtained, which after one crystallisation from aqueous methanol yielded *breienediolone diacetate* in prisms (0·27 g.), m. p. 222—223°, $[\alpha]_D^{17°}$ + 90° (l = 1, c = 1·87). The compound gave no coloration with tetranitromethane in chloroform. *Light absorption in alcohol:* Maxima at 2470 and 3320 A., log ε = 4·094 and 1·672 (Found: C, 75·6, 75·75; H, 10·0, 9·9. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7%).

Breienediolone.—The foregoing compound (170 mg.) was refluxed for 2 hours with 0·1N-alcoholic potassium hydroxide (35 c.c.); the solution was then concentrated to half volume, diluted with water, and extracted with ether. The residue from the washed, dried, and evaporated extract was crystallised from methyl alcohol and then from benzene, yielding rosettes of needles of *breienediolone*, m. p. 247—249° (efferv.), $[\alpha]_D^{21°}$ + 82° (l = 1, c = 1·01) (Found: C, 79·45; H, 10·9. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

Attempted Methylation of Breïn.—A solution of the diol (0·2 g.) in benzene (5 c.c.) was refluxed for 4½ hours with 0·2 g. of "emulsified" potassium in benzene (5 c.c.). Methyl iodide (5 c.c.) was then added, and refluxing continued for a further 3 hours. Alcohol and water were then added, and the precipitated material isolated by extraction with ether. The product, though crystalline, was a mixture which could not be separated; after crystallisation, twice from methanol and twice from acetone, it had m. p. 194—207°, but consisted mainly of unmethylated material (Found: OMe, 1·4%).

Attempted Methylation of Breieneonol-A.—A solution of the keto-alcohol (0·4 g.) in benzene (5 c.c.) was treated successively with potassium and methyl iodide under conditions identical with those described above; the solution rapidly darkened on addition of the potassium. Since only a trace (*ca.* 5 mg.) of crystalline substance (m. p. 199—207°) could be isolated, the whole product (0·4 g.) was refluxed for 10 hours in glacial acetic acid (40 c.c.) with concentrated hydrochloric acid (18 c.c.) and amalgamated zinc dust (18 g.); the product, however, was still an intractable resin.

Methylation of α- and β-Amyrin.—α-Amryin (1 g., dried at 130° in a vacuum) was dissolved in benzene (55 c.c.), the solution mixed with a suspension of emulsified potassium (0·4 g.) in benzene (15 c.c.), and the whole refluxed for 3½ hours. Methyl iodide (10 c.c.) was then added and the refluxing was continued for a further 3 hours. The product, isolated as already described, was crystallised thrice from benzene–alcohol, *α-amyrin methyl ether* separating in lustrous plates (0·25 g.), m. p. 221—222°, $[\alpha]_D^{16°}$ + 93° (l = 1, c = 2·765) (Found: C, 84·3; H, 11·8; OMe, 7·0. $C_{31}H_{52}O$ requires C, 84·45; H, 11·9; OMe, 7·1%).

The methylation of β-amyrin was very incomplete under the above conditions, and unchanged material was easily isolated from the recrystallisation mother-liquors. By the use of smaller quantities of solvent (0·6 g. of the alcohol in 12 c.c. of benzene mixed with 0·4 g. potassium in 10 c.c. of benzene), *β-amyrin methyl ether* was obtained in a yield of 20%; it crystallised from benzene–alcohol in lustrous plates, m. p. 247—248°, $[\alpha]_D^{16°}$ + 98° (l = 1, c = 1·545) (Found: C, 84·1; H, 11·8; OMe, 6·9, 7·1%). Both ethers are considerably less soluble than the parent alcohols.

β-Amyrin p-Toluenesulphonate.—A solution of β-amyrin (0·5 g.) in pyridine (7·5 c.c.) was heated with *p*-toluenesulphonyl chloride (1 g.) on the water-bath for 4 hours; the solution was then diluted with water and extracted with ether. The extract was washed with 2% sodium bicarbonate solution and water, dried, and evaporated. A solution of the residue in acetone deposited dense prisms of the *ester*, m. p. 132—138° (decomp.) (Found: C, 76·5; H, 9·9; S, 5·7. $C_{37}H_{56}O_3S$ requires C, 76·5; H, 9·7; S, 5·5%).

The ester was recovered unchanged from the following experiments: (i) 0·26 G. was refluxed for 4 hours in methyl alcohol (25 c.c.) and benzene (12 c.c.).

(ii) 0·2 G. was refluxed for 2 hours with benzene (5 c.c.) and a 2% solution of concentrated hydrochloric acid in alcohol (30 c.c.). The solution was then made neutral to Congo-red with sodium acetate, the benzene removed, water added, and the precipitate collected and washed.

(iii) 0·19 G. was refluxed for 2 hours with benzene (10 c.c.) and a 10% solution of concentrated hydrochloric acid in alcohol (30 c.c.), the product being isolated as described above.

Finally, the ester (90 mg.) was refluxed for 2 hours with concentrated hydrochloric acid (2 c.c.) in glacial acetic acid (20 c.c.). The solvent was removed under reduced pressure, water added, and the suspension extracted with ether; no crystalline material could be isolated from the resultant resin.

Maniladione.—A solution of maniladiol (1 g.) in 95% acetic acid (150 c.c.) was oxidised with chromic anhydride (0·4 g.) in water (1 c.c.) and acetic acid (49 c.c.), added at room temperature with stirring during 1 hour. After a further hour the product was precipitated with water, filtered off, and dissolved in ether. The extract was washed successively with water, 2% aqueous sodium hydroxide (no acids were present), and water; it was then dried and evaporated. A solution of the residue in aqueous alcohol deposited shining plates (yield, 82%) of *maniladione*, m. p. 209—210°, $[\alpha]_D^{17°}$ + 48° (l = 1, c = 2·39). The compound gave no colour with Schiff's reagent; it gave a yellow colour with tetranitromethane in chloroform, and in the Liebermann–Burchard reaction a pink coloration, changing to orange, was produced. *Light absorption in alcohol :* Maximum at 2925 A., log ε = 1·92 (Found : C, 82·5; H, 10·9. $C_{30}H_{46}O_2$ requires C, 82·1; H, 10·6%).

The *monoxime*, prepared under the usual conditions, separated from aqueous alcohol in shining leaflets, m. p. 272—274° (decomp.) (Found : C, 79·6; H, 10·5; N, 3·2. $C_{30}H_{47}O_2N$ requires C, 79·4; H, 10·5; N, 3·1%).

Oxidation of Maniladione.—The diketone (0·2 g.) was dissolved in 95% acetic acid (20 c.c.) and treated with a solution of chromic anhydride (50 mg.) in water (1 c.c.) and acetic acid (4 c.c.), added during ½ hour at 48—50° with continuous stirring. As no perceptible reaction occurred, the temperature was slowly raised to 63°; oxidation then set in. After being maintained at this temperature for 1 hour, most of the solvent was removed under reduced pressure, and water added to the residue. The precipitate was filtered off, dissolved in ether, and separated into acid and neutral fractions with 2% aqueous sodium hydroxide. Continued crystallisation of the neutral fraction from methyl alcohol gave a yellow product which melted rather indefinitely at 217—222°. The whole of the neutral material was therefore united, dissolved in benzene, and filtered through a column of activated alumina. By this means the mixture was separated into (i) unchanged maniladione, and (ii) a *compound* which crystallised from methanol in bright yellow, prismatic needles, m. p. 227—229·5°, $[\alpha]_D^{18°}$ + 155° (l = 1, c = 1·97) (Found : C, 79·9; H, 9·9. $C_{30}H_{44}O_3$ requires C, 79·6; H, 9·8%).

The alkaline washings from the oxidation were acidified with dilute hydrochloric acid and extracted with ether. The solution was washed, dried, and evaporated, and the residue crystallised twice from aqueous acetic acid, from which the *acid* separated in fluffy needles, m. p. 270—272° (decomp.). Both this acid and also the yellow neutral compound were obtained from an analogous oxidation of maniladiol (Found : C, 73·2; H, 9·6. $C_{30}H_{46}O_5$ requires C, 74·0; H, 9·5%); $[\alpha]_D^{18°}$ + 23° (l = 1, c = 0·51).

Reduction of Maniladione.—(*A*) A solution of the diketone (0·77 g.) in glacial acetic acid (70 c.c.) was refluxed for 10 hours with amalgamated zinc dust (30 g.) and concentrated hydrochloric acid (30 c.c.). The product was isolated as described in the analogous reduction of breienedione; after three crystallisations from acetone there were obtained 90 mg. of prisms which had the constant m. p. 175—176°, $[\alpha]_D^{13°}$ + 32° (l = 1, c = 2·505), but appeared from analysis to be a mixture (Found : C, 86·1; H, 11·9%).

(*B*) The diketone (0·1 g.), hydrazine hydrate (1 c.c. of 95%), and a solution of sodium (0·5 g.) in absolute alcohol (12 c.c.) were heated in a bomb-tube at 190—200° for 16 hours. The reduction product was isolated by extraction with ether, the extract being washed with dilute hydrochloric acid and water, dried, and evaporated. The residual resin was dissolved in benzene (20 c.c.) and filtered through a column (16·5 × 0·9 cm.) of activated alumina. The filtrate contained 70 mg. of crystalline material, which after three crystallisations from aqueous alcohol yielded prisms, m. p. 160—162°, $[\alpha]_D^{22°}$ + 72° ± 10° (l = 1, c = 0·125), in quantity too small for analysis. Concentration of the mother-liquors gave a *substance* which formed rosettes of tiny prisms, m. p. 177—179°, $[\alpha]_D^{22°}$ + 50° (l = 1, c = 1·02); it gave a yellow colour with tetranitromethane in chloroform, and depressed the m. p. of the mixture from the Clemmensen reduction of the diketone (Found : C, 84·0; H, 11·5. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%).

Oxidation of Maniladiol Diacetate.—A solution of the diacetate (0·6 g.) in acetic acid (30 c.c. of 95%) was treated at 95° with a solution of chromic anhydride (0·3 g.) in water (3 c.c.) and acetic acid (12 c.c.), added with stirring during ½ hour. After a further ½ hour the product was precipitated with water and filtered off. It was dissolved in ether, and traces of acid material removed with 2% sodium hydroxide solution. Complete purification of the neutral product by crystallisation was tedious and wasteful; after five crystallisations from methanol the *keto-acetate* was obtained (0·2 g.), m. p. 223—224°, and after several more crystallisations the pure compound separated in needles, m. p. 224—225°, $[\alpha]_D^{16°}$ + 93° (l = 1, c = 1·48), which showed no colour with tetranitromethane (Found : C, 75·65; H, 9·8. $C_{34}H_{52}O_5$ requires C, 75·5; H, 9·7%). *Light absorption in alcohol :* Maxima at 2480 and 3325 A., log ε = 4·059 and 1·625.

Hydrolysis of this diacetate (90 mg., refluxed for 2 hours with 18 c.c. of 0·1N-alcoholic potassium hydroxide, followed by precipitation and ether-extraction) furnished the corresponding *keto-diol*, which crystallised from benzene in rosettes of needles (50 mg.), m. p. 240—241° (efferv.), $[\alpha]_D^{21°}$ + 88° (l = 1, c = 1·29) (Found : C, 79·0; H, 10·85. $C_{30}H_{48}O_3$ requires C, 78·9; H, 10·6%).

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35. *The Oxidation of Hydroxyketostearic Acids in Presence of Alcoholic Alkali.*

By T. P. Hilditch and H. Plimmer.

The disruptive oxidation of mixed 9 : 10-hydroxyketostearic acids in alcoholic alkaline solutions is shown to be mainly dependent upon the excess of potassium hydroxide present. The yields of azelaic acid obtained varied from about 50% in presence of 1 mol. of free caustic alkali to about 75% with 5 mols. of free caustic alkali per mol. of potassium ketolstearates, either at 21° or 50°. With increasing excess of alkali, increasing amounts of 9 : 10-dihydroxystearic acid, m. p. 132°, are found in the products; formation of the dihydroxystearic acid is more evident at 50° than at room temperature in presence of a moderate excess (1—2 mols.) of free alkali. The action proceeds in the absence of actual passage of a stream of oxygen through the solution, and no difference was found when a current of fresh oxygen was replaced by gas circulated through the system from a closed oxygen reservoir.

Experiments have been made with mixed 9 : 10- and 10 : 9-hydroxyketostearic acids prepared from oleic acid in order to ascertain the optimum conditions for the oxidation described by Morrell and Phillips (*J. Soc. Chem. Ind.*, 1938, **57**, 245), who state that continuous circulation of oxygen at room temperature through an alcoholic solution of the salts of the acids in presence of excess of caustic potash gives quantitative yields of azelaic and nonoic acids. We have not succeeded in obtaining quantitative oxidation under any of the conditions which we have tried, but have observed that the yield of azelaic and nonoic acids increases as the excess of alkali present is increased and that, moreover, scission into these acids takes place at 50° in presence of a substantial excess of alkali, without passage of oxygen, to almost the same extent as when oxygen is passed through the solution. We find, further, that the action is complete in 8 hours and does not require the 20 hours stated by Morrell and Phillips, and that little difference results from the use of a stream of fresh oxygen as compared with the recirculation of the same supply of the gas through the liquid system.

The oxidation products were isolated in the following manner. After removal of most of the alcohol the residue was diluted with water, made acid with sulphuric acid, and distilled in steam. The distillate was accurately neutralised with aqueous potash and excess of zinc sulphate solution was added, the precipitated zinc nonoate being filtered off, dried in a vacuum, and characterised by its melting point (133°) and mixed melting point.

The aqueous portion of the residue from the steam-distillation was separated from the oily layer, concentrated to a small bulk, and cooled. The azelaic acid which separated in an almost pure condition was collected, and the filtrate was extracted with ether to obtain the last traces of azelaic acid.

The oily portion of the steam-distillation residue was extracted with boiling light petroleum (b. p. 40—60°), which removed most of the unchanged hydroxyketostearic acids and left a residue which was shown to be mainly 9 : 10-dihydroxystearic acid, m. p. 132°.

The approximate yields of these various products obtained under different conditions of experiment are discussed below. The " percentage scission " is based upon the total yield of crude azelaic acid isolated as described (the recovery of zinc nonoate was insufficiently quantitative for this purpose). The " percentage of unchanged hydroxyketostearic acids " refers to the total material soluble in boiling light petroleum, and that of " crude dihydroxystearic acid " is the percentage of material insoluble in the latter medium.

Experiments at room temperature illustrate the extent to which the disruptive oxidation effected and the amount of dihydroxystearic acid produced are dependent upon the excess of alkali employed (Table I).

Table I.

Oxidation of hydroxyketostearic acids in alcoholic alkaline solution at room temperature.

Expt. No.	Excess KOH, mols.	Oxygen passed.	Temp.	Time (hrs.).	Scission, %.	Dihydroxy-stearic acid, %.	Unchanged material, %.
1	1	Fresh	21°	8	46	3	47
2	1	Circulated	22	20	55	5	41
3	3	Fresh	21	8	58	16	25
4	5	Circulated	21	20	73	16	7
5	5	Fresh	21	8	75	14	5

These results show that at the ordinary temperature the amount of disruptive oxidation into azelaic and nonoic acids is largely a function of the excess of alkali present, whilst the proportion of dihydroxystearic acid obtained also increases when a large excess of caustic potash is present. Experiments carried out at 50° led to the same conclusions, and also showed that the passage of gaseous oxygen is not essential for the production of azelaic and nonoic acids from the hydroxyketostearic acids (Table II).

TABLE II.

Oxidation of the hydroxyketostearic acids in alcoholic alkaline solution at 50°.

Expt. No.	Excess KOH, mols.	Oxygen passed.	Time (hrs.).	Scission, %.	Dihydroxy-stearic acid, %.	Unchanged material, %.
6	1	Fresh	8	50	41	7
7	2	None	8	61	30	8
8	5	Fresh	8	72	17	10

It will be noted that, with only 1 mol. excess of caustic alkali, the yield of scission products remains at about the same level at 50° as at 21° (expt. 1, Table I), but that nearly all the hydroxyketostearic acids disappeared at 50°, considerable proportions of dihydroxystearic acid being produced. With higher concentrations of alkali at 50°, the total amount of hydroxyketostearic acids attacked remained little altered, but more scission products and less dihydroxystearic acid were obtained. The passage of gaseous oxygen seems to be of little importance.

In order to ascertain whether the low yields of azelaic and nonoic acids obtained in presence of a comparatively small excess of free caustic alkali were due to preferential oxidation of one of the two isomeric hydroxyketostearic acids, the unchanged residue from one of the experiments (Table I, no. 2) was used in a subsequent experiment (no. 3); it was then found that the action proceeded normally. This is in accordance with the statement by Morrell (*Fette u. Seifen*, 1939, **46**, 546) that, whilst 9-hydroxy-10-ketostearic acid is preferentially oxidised in alkaline solution, tautomeric change of the 10-hydroxy-9-ketostearic acid to the 9-hydroxy-10-keto-form (cf. Stevens, *J. Amer. Chem. Soc.*, 1939, **61**, 1714) proceeds under these conditions, and disruptive oxidation of the whole of the acids eventually takes place.

It is clear that, even with 5 mols. excess of potassium hydroxide per mol. of the potassium salts of the hydroxyketostearic acids, not more than 75% of the latter are broken down into azelaic and nonoic acids; and it would appear that an excess of at least 10—12 mols. of free alkali would be required before quantitative conversion into the scission products could be effected under these conditions.

The formation of dihydroxystearic acid, which is clearly also favoured by increased proportions of caustic potash in the reacting system, may possibly be explained as the result of a reaction: 2-CH(OH)·CO· $\longrightarrow$ –CO·CO– + –CH(OH)·CH(OH)–, whilst the further breakdown into azelaic and nonoic acids may result from decomposition either of the original hydroxyketostearic acids or of diketostearic acid produced in the manner suggested. It appears reasonable to suggest that the 9 : 10-dihydroxystearic acid, m. p. 132°, which has frequently been observed to form a small proportion of the products of atmospheric oxidation of oleic acid (cf., *e.g.*, Skellon, *J. Soc. Chem. Ind.*, 1931, **50**, 382T) may arise from a similar decomposition of hydroxyketostearic acids produced from the peroxides initially formed (Ellis, *J. Soc. Chem. Ind.*, 1926, **45**, 193T). It is known that diketostearic acid derivatives are simultaneously produced, and give rise to a yellowish colour in oxidised oil films. Further, this appears to offer a reasonable explanation of the well-established fact that the 9 : 10-dihydroxystearic acid of m. p. 132° is produced during atmospheric oxidation, whereas the lower-melting form (m. p. 95°) would be expected to result by direct addition of oxygen [the form melting at 132° being produced directly from oleic acid only as the result of alkaline (permanganate) oxidation].

EXPERIMENTAL.

Preparation of the Mixed Hydroxyketostearic Acids.—This was essentially the same as that recommended by King (J., 1936, 1788), based on the earlier work of Holde and Marcusson (*Ber.*, 1903, **36**, 2657), but modifications in detail were made in order to reduce the large volumes of solution requisite in the preparation of more than small specimens of the α-ketolstearic acids; this involved some loss in yield of the latter as compared with the conditions used by King.

Purified oleic acid (50 g.) was neutralised with aqueous potassium hydroxide, and the solution of potassium oleate diluted with water and crushed ice to 7500 c.c. A 2% solution of potassium permanganate (2500 c.c.) was then added to the mechanically stirred solution at 0°, with further crushed ice (1000 c.c.) during 10 minutes. Stirring was continued for a further 10 minutes, and the solution allowed to stand at 0° for 18 hours; it was then decolourised by addition of sodium bisulphite (300 g.) in water (750 c.c.), and the acids liberated by addition of concentrated hydrochloric acid (500 c.c.). The white, flocculent precipitate of solid acids was collected, washed with a little water, and dried in a vacuum. The dried product was digested with chloroform (500 c.c.), and the solution cooled at 0°; a little 9 : 10-dihydroxystearic acid (0·6 g.) then separated and was removed. The residue (34·9 g.) from the evaporated chloroform filtrate was dissolved in boiling light petroleum (b. p. 40—60°, 3500 c.c.), yielding a yellow solution which deposited crude α-ketolstearic acids (21·2 g., m. p. 66—69·5°) on keeping at 0°. The light petroleum mother-liquors gave a solid yellow residue (12·8 g.) on evaporation.

When the crude hydroxyketostearic acids were again treated with chloroform, a further 0·8 g. of 9 : 10-dihydroxystearic acid was separated; the chloroform-soluble portion, after another crystallisation from light petroleum, gave 18·1 g. of still impure α-ketolstearic acids (m. p. 67—71°). Crystallisation of this from 60% alcohol finally yielded four fractions: diketostearic acid (1·5 g., m. p. 84—86°), a mixture of α-ketol- and diketostearic acids (2·8 g., m. p. 66—85°), somewhat impure α-ketolstearic acids (6·3 g., m. p. 59—63°), and a comparatively pure specimen of the mixed α-ketolstearic acids (4·6 g., m. p. 63—65°) (Found: OH, 5·1, 5·3; CO, 8·7, 9·4. Calc.: OH, 5·4; CO, 8·9%).

Oxidation of the Mixed 9 : 10-*Hydroxyketostearic Acids.*—The general description already given of the isolation of the products of oxidation may be illustrated by details of two experiments carried out respectively at room temperature and at 50° with fresh oxygen.

(a) *Oxidation at* 21° *with fresh oxygen* (Expt. 1, Table I). The mixed α-ketolstearic acids (2·5 g.) were dissolved in 0·25N-alcoholic potassium hydroxide solution (64 c.c., 100% excess), and the solution diluted with alcohol (66 c.c.) and placed in a three-necked flask fitted with a mechanical stirrer, thermometer and gas inlet and outlet tubes. Fresh oxygen was bubbled through the mechanically stirred solution at room temperature (21°) for 8 hours; the temperature rose to 24° during the first hour and subsequently slowly returned to that of the room. The product was worked up according to the scheme previously described (p. 204). The aqueous distillate (4 l.) from the steam-distillation was exactly neutralised with potassium hydroxide solution; excess of zinc sulphate solution then precipitated zinc nonoate (0·32 g.). The hot aqueous portion of the residue in the steam-distillation flask, together with the liquor from two washings of the oily portion with boiling water, after concentration and cooling, deposited azelaic acid (0·61 g.); the cold filtrate yielded to ether a further amount (0·08 g.) of azelaic acid. The total weight of azelaic acid recovered was 46% of that demanded for complete scission of the ketolstearic acids originally present. Boiling light petroleum (b. p. 40—60°) left undissolved 0·07 g. of material from the oily layer; the solution on cooling deposited crude hydroxyketostearic acids (0·99 g., m. p. 58—63°) and retained 0·18 g. of less pure, yellowish solid acids. The approximate yield of dihydroxystearic acid was thus less than 3%, and of unchanged material (including any uncharacterised by-products soluble in light petroleum) 47%.

(b) *Oxidation at* 50° *with fresh oxygen* (Expt. 6, Table II). The mixed α-ketolstearic acids (5 g.) were dissolved in 0·25N-alcoholic potassium hydroxide solution (130 c.c., 100% excess) and placed in the reaction-flask, which was maintained at 50° in an oil-bath, a current of fresh oxygen being bubbled through the mechanically stirred solution as described above for 8 hours. After steam-distillation of the acidified products, the amount of zinc nonoate deposited from the neutralised aqueous distillate was 1·07 g.; the hot aqueous portion (and washings) of the residue from the steam-distillation, on cooling, deposited 1·27 g. of azelaic acid and then yielded a further 0·23 g. of the acid on extraction of the cold mother-liquors with ether (total yield of azelaic acid 1·5 g., equivalent to 50% of the theoretical). From the oily portion of the residue (2·74 g.) there were obtained 2·05 g. of material insoluble in light petroleum, which on recrystallisation from ethyl acetate melted at 132° and was 9 : 10-dihydroxystearic acid (mixed m. p. unchanged); the light petroleum solution deposited 0·13 g. of crude ketolstearic acids and yielded on evaporation a further 0·23 g. of viscous residue (yield of dihydroxystearic acid, *ca.* 41%; of unchanged or indefinitely characterised products, 7%).

In the experiments (Table I, nos. 2 and 4) in which the oxygen was re-circulated through the solution, the oxygen inlet and outlet tubes were connected with a closed oxygen reservoir and a circulation pump, by means of which the same supply of oxygen was made to flow continuously through the alkaline solutions.

We desire to thank Imperial Chemical Industries, Ltd. (Dyestuffs Group), for a grant in aid of this investigation.

THE UNIVERSITY, LIVERPOOL. [*Received, November* 21*st*, 1941.]

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36. 1 : 3 : 3-*Trimethyl*-Δ^1-cyclo*hexene*-4-*carboxylic Acid: its Formation from* l-Δ^3-*Carene*-5 : 6-*epoxide.*

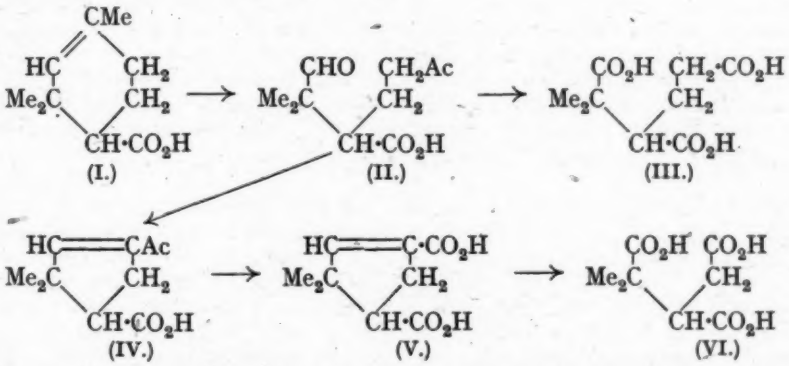
By A. R. PENFOLD and J. L. SIMONSEN.

The acid, $C_{10}H_{16}O_2$, formed by the action of cold ethyl-alcoholic potassium hydroxide on *l*-Δ^3-carene-5 : 6-epoxide (VII) has been shown to be 1 : 3 : 3-*trimethyl*-Δ^1-cyclo*hexene*-4-*carboxylic acid* (I) by its oxidation to β-methylpentane-βγε-tricarboxylic acid (III). A further product of the oxidation was 1 : 1-*dimethyl*-Δ^2-cyclo*pentene*-3 : 5-*dicarboxylic acid* (V), which gave on ozonolysis β-methylbutane-βγδ-tricarboxylic acid (VI).

THE suggestion (Penfold, Ramage, and Simonsen, J., 1939, 1501) that the acid, $C_{10}H_{16}O_2$, m. p. 83°, formed by the action of cold ethyl-alcoholic potassium hydroxide on *l*-Δ^3-carene-5 : 6-epoxide (VII) was one of the optically active modifications of *dl*-Δ^2-*cyclo*geranic acid was disproved by Bennett, Ramage,

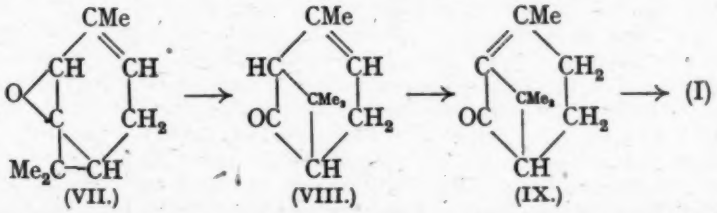
and Simonsen (J., 1940, 418). We have now determined the structure of the acid by an investigation of its degradation products.

On ozonolysis it yielded a liquid acid, which reacted readily with carbonyl reagents. A *semicarbazone*, $C_{11}H_{17}O_3N_3$, decomp. 252°, was prepared, but purification could not be thus effected. An alkaline solution of the acid was therefore oxidised with sodium hypobromite: two crystalline acids were obtained, (*A*), $C_9H_{12}O_4$, m. p. 198—199°, and (*B*), m. p. *ca.* 141°. The acid (*B*) gave on analysis figures agreeing approximately with the formula $C_9H_{14}O_6$ and it was thought at first that it might be identical with β-methylpentane-βδε-tricarboxylic acid, which according to Roberts (*J. Amer. Chem. Soc.*, 1926, **28**, 1975) melts at this temperature (see below). On further purification, however, the melting point of the acid was raised to 153° and it was found by direct comparison to be identical with β-methylpentane-βγε-tricarboxylic acid (III). The formation of this acid from the unsaturated cyclic acid left no doubt that the latter must be represented by (I).



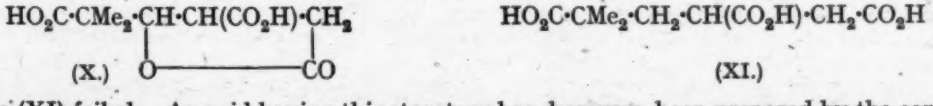
The acid (*A*), which was sparingly soluble in water and was optically active, was unstable to potassium permanganate in alkaline solution. On ozonolysis it gave β-methylbutane-βγδ-tricarboxylic acid (VI) and therefore it is 1 : 1-*dimethyl*-Δ²-cyclo*pentene*-3 : 5-*dicarboxylic acid* (V). This acid is formed by the cyclisation of the primary ozonolysis product, the keto-aldehyde (II), to the unsaturated keto-acid (IV), which is oxidised by sodium hypobromite to (V). The semicarbazone, decomp. 252°, referred to above is derived from (IV).

The formation of the *cyclo*hexene acid from the epoxide (VII) is undoubtedly connected with the marked tendency which the latter exhibits to isomerise to ketones (compare Penfold, Ramage, and Simonsen,



loc. cit., p. 1497). This isomerisation may result in the formation of the bicyclic ketone (VIII), in which, under the influence of the alkali, the ethylenic linkage will tend to pass into the αβ-position, yielding the unstable ketone (IX); this on hydration gives (I). The fact that the cyclic acid (I) has the ethylenic linkage in the Δ¹-position lends support to this interpretation of the mechanism of the reaction.

As mentioned above, it was at first regarded as possible that the acid (*B*) might be identical with β-methylpentane-βδε-tricarboxylic acid (XI). Roberts (*loc. cit.*) records the preparation of an acid having this structure by the reduction of the lactone of γ-hydroxy-β-methylpentane-βδε-tricarboxylic acid (X), m. p. 145°. We had no difficulty in preparing the lactone by Roberts's procedure, but all attempts to



reduce it to (XI) failed. An acid having this structure has, however, been prepared by the condensation of ethyl sodiomalonate with ethyl γ-bromo-αα-dimethylglutarate, followed by the hydrolysis of the *tetracarboxylic ester* so obtained. The acid prepared in this manner had m. p. 180° and there can therefore

be little doubt that Roberts's acid, m. p. 141°, was actually a somewhat impure specimen of the original lactone.

Experimental.

Ozonolysis of 1 : 3 : 3-*Trimethyl*-Δ^1-cyclo*hexene*-4-*carboxylic Acid.*—The acid (2·9 g.) in methyl acetate (25 c.c.) was ozonised at 0°, the issuing gases being passed through water. Formaldehyde was absent from the wash water. After removal of the solvent under diminished pressure the ozonide was decomposed by heating with water (5 c.c.) on the water-bath for 1 hour. On evaporation the solution gave a gum, from which a small amount of a crystalline acid, m. p. *ca.* 50—70°, separated; it could not be purified. A *semicarbazone* was prepared which was very sparingly soluble in alcohol and crystallised from dilute acetic acid in small plates, decomp. 252° (Found: C, 55·8; H, 7·0; N, 17·7. $C_{11}H_{17}O_3N_3$ requires C, 55·2; H, 7·1; N, 17·6%).

The liquid acid (1·7 g.) obtained by evaporation of the aqueous solution was dissolved in dilute aqueous sodium hydroxide and oxidised with aqueous sodium hypobromite (NaOH, 4 g.; Br_2, 1·6 c.c.) at 0°, bromoform separating immediately. After 1 hour the bromoform was removed, the excess of hypobromite destroyed with sulphur dioxide, the solution concentrated, and the acid products isolated by ether. The oil obtained partly crystallised and after trituration with hydrochloric acid the solid was collected. This, on fractional crystallisation from water, gave a sparingly soluble acid (*A*), separating in bayonet-shaped needles, m. p. 197°, raised to 198—199° by two further crystallisations from water (Found: C, 58·8; H, 6·5. $C_9H_{12}O_4$ requires C, 58·7; H, 6·5%). 1 : 1-*Dimethyl*-Δ^2-cyclo*pentene*-3 : 5-*dicarboxylic acid* had $[\alpha]_{5461}$ −15° in acetone (*c*, 2·0).

The aqueous solution from which the acid (*A*) had been deposited gave on saturation with hydrogen chloride a more soluble acid (*B*), m. p. 137°, raised to 140—141° by two further crystallisations from hydrochloric acid (Found: C, 50·0; H, 6·6. Calc. for $C_9H_{14}O_6$: C, 49·5; H, 6·4%). After further purification through its sparingly soluble copper salt, prepared by the addition of copper acetate to its aqueous solution, the acid after crystallisation from hydrochloric acid had m. p. 153° both alone and in admixture with authentic β-methylpentane-βγε-tricarboxylic acid (Found: C, 49·4; H, 6·4%).

The mixture of liquid acids remaining after the separation of the acids (*A*) and (*B*) was oxidised with nitric acid (*d* 1·4) on the water-bath. The acid remaining after the removal of the excess of mineral acid solidified on trituration with formic acid and after crystallisation from water had m. p. 147°, raised to 150° on admixture with β-methylbutane-βγδ-tricarboxylic acid.

Ozonolysis of 1 : 1-*Dimethyl*-Δ^2-cyclo*pentene*-3 : 5-*dicarboxylic Acid.*—The acid (0·4 g.) in methyl acetate (20 c.c.) was ozonised at 0°. The oxidation proceeded rapidly and after removal of the solvent in a vacuum the ozonide was, after dilution with water (5 c.c.), decomposed by heating on the water-bath for 1 hour. The solution was made alkaline with sodium carbonate, hydrogen peroxide (2 c.c.; 20-vol.) added, and the mixture kept overnight. The alkaline solution was concentrated, acidified with hydrochloric acid, and evaporated to dryness, and the residue extracted with acetone. Evaporation of the solvent left a solid (0·5 g.), which crystallised readily from hydrochloric acid or benzene–acetone in thin plates, m. p. 143°, raised to 150—151° by repeated crystallisation. This m. p. was not depressed by β-methylbutane-βγδ-tricarboxylic acid (Found: C, 47·0; H, 6·0. Calc. for $C_8H_{12}O_6$: C, 47·1; H, 5·9%). The acid was optically inactive.

β-*Methylpentane*-βδε-*tricarboxylic Acid.*—The keto-ester, ethyl β-methylpentan-γ-one-βδε-tricarboxylate, prepared as described by Roberts (*loc. cit.*), was a mobile, pale yellow oil, b. p. 184°/16 mm., $n_D^{17°}$ 1·458 (Found: C, 57·4; H, 7·8. Calc. for $C_{15}H_{24}O_7$: C, 56·9; H, 7·6%). Reduction of the keto-ester (14 g.) to the hydroxy-ester was readily effected in ethereal solution with aluminium amalgam (Al, 20 g.). The ester was a colourless oil which gave no ferric chloride reaction. After digestion with hydriodic acid (40 g., *d* 1·94) and red phosphorus (2 g.) for 8 hours, evaporation of the filtered solution gave an oil which rapidly crystallised. The lactone of γ-hydroxy-β-methylpentane-βδε-tricarboxylic acid separated from ether or acetone–benzene in rosettes of needles, m. p. 145—146° (Found: C, 50·0; H, 5·8; *M*, 217·7. Calc. for $C_9H_{12}O_6$: C, 50·0; H, 5·6%; *M*, 216). Other attempts to reduce the lactone by heating with hydriodic acid (*d* 1·7) and red phosphorus at 160° or by the method of Miescher and Billeter (*Helv. Chim. Acta*, 1939, **22**, 601) failed.

Condensation of Ethyl γ-*Bromo*-αα-*dimethylglutarate and Ethyl Sodiomalonate. Ethyl* β-*Methylpentane*-βδεε-*tetracarboxylate.*—αα-Dimethylglutaric acid was prepared by the ozonolysis of *iso*lauronolic acid, followed by oxidation with sodium hypobromite as described by Haworth and Perkin (J., 1908, **83**, 588). Ethyl γ-bromo-αα-dimethylglutarate had b. p. 155—160°/26 mm.; Perkin (J., 1902, **81**, 252) gives 165—170°/35 mm. To a suspension of ethyl sodiomalonate (from ethyl malonate, 16 g.) in alcohol (50 c.c.), the bromo-ester (29·5 g.) was cautiously added, rise of temperature being prevented by cooling in ice-water. After being kept overnight, the mixture, from which much sodium bromide had separated, was heated on the water-bath for 1 hour to complete the reaction. The *tetracarboxylic ester* (20 g.), a somewhat viscid oil, isolated in the usual manner, had b. p. 210—216°/25 mm. (Found: C, 57·9; H, 7·9. $C_{18}H_{30}O_8$ requires C, 57·8; H, 8·0%). Digestion of the ester (3 g.) with hydrochloric acid (15 c.c.) gave β-*methylpentane*-βδε-*tricarboxylic acid*, m. p. 180°, unchanged by crystallisation from hot water, from which the acid separated in hexagonal prisms (Found: C, 49·8; H, 6·7; *M*, 219·7. $C_9H_{14}O_6$ requires C, 49·5; H, 6·4%; *M*, 218). The acid was somewhat sparingly soluble in

water and in the ordinary organic solvents with the exception of alcohol and acetic acid; addition of copper acetate to its aqueous solution precipitated a sparingly soluble copper salt. The *quinine* salt crystallised from dilute alcohol in balls of needles, m. p. 199—201°, $[\alpha]_{5461}$ −160° in alcohol (*c*, 1·0) (Found: C, 66·9; H, 7·2. $C_9H_{14}O_6,2C_{20}H_{24}O_2N_2,H_2O$ requires C, 66·5; H, 7·2%). The rotatory power of the salt was unaltered by further crystallisation.

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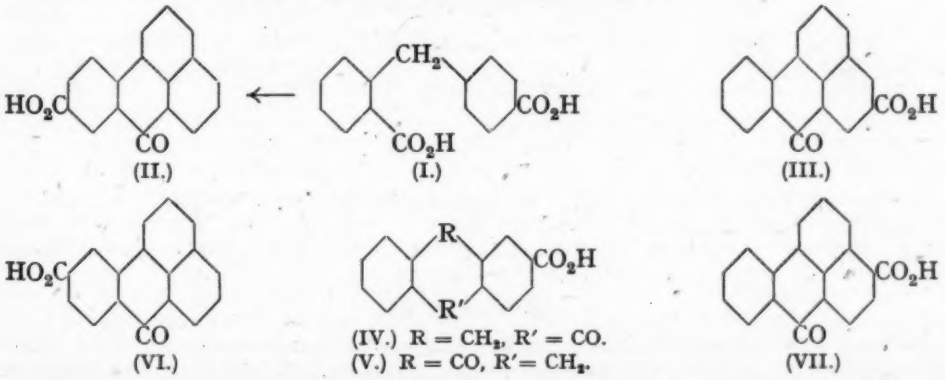
37. meso*Benzanthronecarboxylic Acids.*

By F. C. COPP and J. L. SIMONSEN.

The *meso*benzanthronecarboxylic acids prepared by the condensation of glycerol with diphenylmethane-2 : 4′-dicarboxylic acid and with the anthrone of anthraquinone-2-carboxylic acid have been examined. The former condensation yields *meso*benzanthrone-9-carboxylic acid, and the latter gives a mixture of the 9- and the 10-acid. Attempts to condense the anthrone of anthraquinone-1-carboxylic acid with glycerol failed, but the amide can be condensed. The amide of *meso*benzanthrone-11-carboxylic acid formed the main product of the reaction, together with a small quantity of the 8-acid.

OF the ten theoretically possible *meso*benzanthronecarboxylic acids, five have so far been described and rigidly oriented, namely, the 1-, 2-, 3-, 4- and 11-acids. By the condensation of diphenylmethane-2 : 4′-dicarboxylic acid (I) with glycerol in the presence of sulphuric acid Schaarschmidt (G.P. 251,480, 254,023; Friedländer's "Fortschritte," Vol. 11, 703) prepared a *meso*benzanthronecarboxylic acid stated to be the 9-acid (II) (Beilstein's "Organische Chemie," Ergänzungsband, **10**, 382), although from its method of preparation it can equally well be the 5-acid (III). Schaarschmidt prepared also an isomeric acid by the condensation of the anthrone of anthraquinone-2-carboxylic acid with glycerol. This acid is assumed to be the 10-acid (VI), although the condensation can yield either the 9- (II), 5- (III) or 4- (VII acid depending upon whether the anthrone has the structure (IV) or (V).



Reinvestigating these two glycerol condensations, we have found that the first yields a homogeneous product consisting of the 9-acid, and the second gives a mixture of the 9- and the 10-acid. The acid from the first condensation, characterised by the preparation of the *methyl* and the *ethyl* ester, has been shown to be the 9-acid by two distinct methods. By the Schmidt reaction (G.P. 307,798; von Braun, *Annalen*, 1931, **490**, 125; Boyes, Grieve, and Rule, J., 1938, 1834) the acid was converted into an *amino*meso*benzanthrone*, yielding on diazotisation and treatment with cuprous chloride 9-chloro*meso*benzanthrone. It followed, therefore, that the carboxyl and the amino-group were in the 9-position. Confirmation of the structure assigned to the acid was obtained by its preparation from 9-methyl*meso*benzanthrone by oxidation of the alkyl group with selenium dioxide, the aldehyde, which formed the main product of the reaction, being further oxidised to the acid by potassium permanganate in pyridine solution.

The condensation of the anthrone of anthraquinone-2-carboxylic acid proceeded much less smoothly and gave a complex mixture of acids, which was resolved by chromatographing the ethyl esters. This

resulted in the separation of (i) ethyl anthraquinone-2-carboxylate, (ii) ethyl *meso*benzanthrone-9-carboxylate, and (iii) in small amount an ethyl *meso*benzanthronecarboxylate, m. p. 137—139°. The last ester gave on hydrolysis an *acid*, m. p. 326—327°, yielding a *methyl* ester, m. p. 167—168°. For the purposes of comparison *meso*benzanthrone-4-carboxylic acid (VII), m. p. 314—315°, was prepared from 4-methyl*meso*benzanthrone (I.G., B.P. 277,670) and characterised by the preparation of its *methyl* ester, m. p. 215—216°, and its *ethyl* ester, m. p. 134—135°. The melting points of the methyl esters showed that the two acids were not identical and this was confirmed by the two ethyl esters in admixture showing a marked depression in m. p. Further the 4-acid dissolved in sulphuric acid to give a deep red non-fluorescent solution in marked contrast to the pink solution of the new acid with its strong yellowish-green fluorescence. The structure of the latter acid as meso*benzanthrone*-10-*carboxylic acid* (VI) was established by the direct comparison of the acid and its derivatives with specimens of this acid and its esters prepared by the oxidation of 10-methyl*meso*benzanthrone.

In view of these results it appeared of interest to investigate the condensation of anthraquinone-1-carboxylic acid or its anthrone with glycerol, since this could theoretically yield either the 6-, 8- or 11-carboxylic acid. It was found, however, that neither anthraquinone-1-carboxylic acid nor its anthrone (Barnett, Cook, and Grainger, *Ber.*, 1924, **57**, 1777) would condense with glycerol. Since it appeared possible that this failure might be due to lactonisation, the amide was utilised in place of the free acid. This derivative condensed readily under the conditions given on p. 212 to yield a mixture of acid and neutral products. The acid, obtained in small yield, after purification through its *methyl* ester, had m. p. 254—255° and was identified as meso*benzanthrone*-8-*carboxylic acid* by oxidation with chromic acid to anthraquinone-1 : 5-dicarboxylic acid.

The main product of the condensation, insoluble in aqueous sodium carbonate, crystallised from nitrobenzene in yellow needles. Analysis showed this to be the amide of a *meso*benzanthronecarboxylic acid and it gave on hydrolysis an acid, m. p. 267—268°, methyl ester, m. p. 160—161°. This acid was found to be the 11-carboxylic acid by direct comparison with a specimen for which we are indebted to Dr. Rule.

Condensations with the glycerol occur in the unsubstituted anthraquinone ring, as would perhaps be expected on general theoretical grounds. In the appended table we give the melting points of the *meso*benzanthronecarboxylic acids and their esters so far as they are known. Only the 5- and the 6-carboxylic acid have still to be prepared.

meso*Benzanthronemonocarboxylic Acids.*

CO_2H.	M. p.	Me ester, m. p.	Et ester, m. p.	CO_2H.	M. p.	Me ester, m. p.	Et ester, m. p.
1	285° [1]	—	—	4	*314—315°*	*215—216°*	*134—135°*
2	347 [2]	—	172—173°	8	*254—255*	*173·5—174·5*	—
	342 [3]	—	—	9	*352—354*	*188—189*	*172·5—173·5*
3	335 [4, 5]	—	—	10	*326—327*	*167—168*	*137—139*
4	307—308 [4]	—	—	11	273 [7]	159 [8]	—
	295 [6]	—	—		*267—268*	*160—161*	—

[1] Boyes, Grieve, and Rule, J., 1938, 1833. [2] Schaarschmidt, *Ber.*, 1917, **50**, 294. [3] Heilbron, Hislop, and Irving, J., 1936, 781. [4] B.P. 277,670. [5] U.S.P. 1,740,771. [6] B.P. 321,916; F.P. 671,399. [7] Rule, Pursell, and Bennett, J., 1935, 570. [8] Bigelow and Rule, *ibid.*, p. 574. M. p.'s in italics are our determinations.

Experimental.

Diphenylmethane-2 : 4′-*dicarboxylic Acid.*—The following method is more convenient than that of Limpricht (*Annalen*, 1899, **309**, 98). A mixture of benzophenone-2 : 4′-dicarboxylic acid (35 g.), amalgamated zinc wool (120 g.), hydrochloric acid (200 c.c.), water (50 c.c.), and anisole (200 c.c.) was refluxed for 30 hours, further hydrochloric acid (40 c.c.) being added at eight-hourly intervals. After removal of the anisole in steam the diphenylmethane-2 : 4′-dicarboxylic acid, with a little unchanged zinc, was collected from the cooled solution, the acid dissolved in aqueous sodium carbonate, and the filtered solution acidified. The acid (32 g.), which was pure enough for further experiments, crystallised from acetic acid in needles, m. p. 219—220° (Found: *M*, 252. Calc. for $C_{15}H_{12}O_4$: *M*, 256).

meso*Benzanthrone*-9-*carboxylic Acid.*—(1) *Condensation of diphenylmethane*-2 : 4′-*dicarboxylic acid and glycerol.* To a solution of the acid (10 g.) in sulphuric acid (90%; $d^{15°}$ 1·820; 300 c.c.) at 76°, glycerol (15 c.c.) was added (mechanical stirring). The temperature rose to 94° and a green fluorescence developed. After being kept at 100—120° for 45 minutes, the mixture was cooled and poured into water (1 l.) and the solid which separated was collected. The crude acid was digested with aqueous sodium carbonate (charcoal), the filtered solution acidified, and the acid (7 g.) collected. After digestion with alcohol to remove readily soluble impurities the acid was esterified *via* the acid chloride. The *ethyl* ester crystallised from ethyl acetate in long yellow

needles, m. p. 172·5—173·5° (Found: C, 79·0; H, 5·1. $C_{20}H_{14}O_3$ requires C, 79·5; H, 4·6%), and the *methyl* ester from methyl alcohol in yellow needles, m. p. 188—189° (Found: C, 78·7; 4·1. $C_{19}H_{12}O_3$ requires C, 79·2; H, 4·1%).

meso*Benzanthrone*-9-*carboxylic acid*, obtained by hydrolysis of the ethyl ester with methyl-alcoholic potassium hydroxide solution, crystallised from nitrobenzene in long yellow needles, m. p. 352—354° (Found: C, 78·7; H, 3·9. $C_{18}H_{10}O_3$ requires C, 78·8; H, 3·6%). The acid dissolved in alkali to give a yellow solution with a brilliant emerald-green fluorescence; the potassium salt was somewhat sparingly soluble in water. The solution of the acid in sulphuric acid was canary-yellow with a green fluorescence.

(2) *Oxidation of* 9-*methyl*meso*benzanthrone*. A mixture of the benzanthrone (4·8 g.), selenium dioxide (2·2 g.), and water (20 c.c.) was heated in a rotatory autoclave at 230—240° for 2 hours. The solid was collected and digested with hot acetic acid, and the filtered solution poured into water. The precipitated solid was digested with hot aqueous sodium carbonate, and the filtered solution acidified, yielding the acid (0·5 g.). The residue (4 g.) insoluble in alkali consisted of unchanged benzanthrone and an aldehyde; the percentage of the latter, estimated as semicarbazone, was approximately 24%. For the preparation of a further quantity of the acid the crude solid (3 g.) was dissolved in pyridine (50 c.c.), and finely divided potassium permanganate (0·3 g.) added during ½ hour (mechanical stirring). The filtered solution was diluted with water and acidified, giving crude *meso*benzanthrone-9-carboxylic acid (0·7 g.). The acid, after crystallisation from nitrobenzene, had m. p. 320—330°; the ethyl ester had m. p. 172—173°, both alone and in admixture with the ethyl ester of the acid prepared as described in section (1).

9-*Amino- and* 9-*Chloro*-meso*benzanthrones*.—To a solution of *meso*benzanthrone-9-carboxylic acid (3 g.) in sulphuric acid (30 c.c.) and chloroform (30 c.c.) maintained at 40—50°, sodium azide (5 g.) was added during 7 hours, chloroform (20 c.c.) being added to replace loss by evaporation (mechanical stirring). The cooled mixture was poured into water, the chloroform removed in steam, and the solid collected. After digestion with aqueous sodium carbonate the crude amine (0·7 g.) was obtained as a red powder; unchanged acid (2·1 g.) was recovered from the sodium carbonate solution. 9-*Amino*meso*benzanthrone* crystallised from *o*-dichlorobenzene in red needles having a metallic lustre, m. p. 216—217° (Found: C, 82·9; H, 4·8. $C_{17}H_{11}ON$ requires C, 83·3; H, 4·5%). The amine is a weak base, being insoluble in dilute mineral acids; it dissolved in hot hydrochloric acid and the cooled solution deposited a sparingly soluble, yellow hydrochloride. The base dissolved in sulphuric acid to give a greenish-yellow solution having a faint green fluorescence. The *acetyl* derivative crystallised from acetic acid in deep yellow needles, m. p. 252—254° (Found: C, 79·1; H, 4·8. $C_{19}H_{13}O_2N$ requires C, 79·4; H, 4·6%).

For conversion into 9-chloro*meso*benzanthrone a solution of the amine (0·5 g.) in concentrated sulphuric acid (10 c.c.) at 0—5° was gradually treated with powdered sodium nitrite (0·2 g.). After remaining at 0° for 2 hours, the mixture was cooled in salt–ice and cautiously diluted with water (20 c.c.); precipitation of the sparingly soluble diazonium sulphate was completed by the addition of sodium sulphate. The diazonium salt was collected and made into a paste with hydrochloric acid (10 c.c.), and the mixture added gradually to hydrochloric acid (30 c.c.) containing cuprous chloride (1 g.), the temperature being maintained at 30—35°. After 3 hours the temperature was raised to 80°, the mixture cooled, and the crude chloro*meso*benzanthrone collected. The solid was digested with acetic acid to remove copper salts, with alkali to remove phenols, and sublimed in a high vacuum, giving yellow needles (0·1 g.), m. p. 182—184°, raised to 186° by crystallisation from acetic acid. This m. p. was unchanged by authentic 9-chloro*meso*benzanthrone.

Condensation of Anthraquinone-2-carboxylic Acid and Glycerol. meso*Benzanthrone*-9- *and* -10-*carboxylic Acids*.—A mixture of the anthraquinone acid (10 g.), sulphuric acid (300 c.c.; 90%, $d^{15°}$ 1·820), copper bronze (2 g.), a trace of zinc dust, and glycerol (10 c.c.) was heated at 110° for 1 hour and at 120° for 15 minutes (mechanical stirring). The cooled mixture was poured into water, the solid collected and digested with aqueous sodium carbonate, and the filtered alkaline solution acidified. The crude acid (8·6 g.) which separated was collected, dried, and extracted with hot nitrobenzene, which left undissolved a black solid; the nitrobenzene deposited an acid (2·9 g.) in brownish-yellow needles having an indefinite m. p. For purification the acid (6·2 g.) was converted into the silver salt and this was esterified with ethyl iodide in benzene solution.* The resulting ester (5·5 g.), m. p. 145—172°, gave in sulphuric acid a red solution with a green fluorescence. The ester, in benzene solution, was chromatographed, an alumina tower being used which had been previously washed with phenol to diminish the alkalinity. The ester (0·5 g.) was thus readily separated into two fractions: (*a*) a fraction (0·3 g.), m. p. 169—171°, adsorbed by the alumina, and (*b*) a yellow gum (0·15 g.) which passed through. Fraction (*a*), after crystallisation from alcohol, had m. p. 172·5—173·5°, both alone and in admixture with ethyl *meso*benzanthrone-9-carboxylate. Fraction (*b*) was rechromatographed and thus separated into a more soluble fraction consisting of ethyl anthraquinone-2-carboxylate and an ester crystallising from alcohol in light yellow needles, m. p. 136—138° after softening at 134°. From a concentrated alcoholic solution *ethyl* meso*benzanthrone*-10-*carboxylate* crystallised in deep golden needles, but the m. p. was unchanged (Found: C, 79·1; H, 4·6. $C_{20}H_{14}O_3$ requires C, 79·5; H, 4·6%). The *acid*, obtained by the hydrolysis of the ester with methyl-alcoholic potassium hydroxide solution and separated as the sparingly soluble, yellow potassium salt,

* If the acid was esterified *via* the acid chloride, prepared by the action of thionyl chloride, chloro-esters were formed probably from the anthraquinone acid present in the mixture.

crystallised from nitrobenzene in yellow needles, m. p. 326—327°, both alone and in admixture with the acid prepared from 10-methyl*meso*benzanthrone (see below) (Found: C, 78·4; H, 3·7. $C_{18}H_{10}O_3$ requires C, 78·8; H, 3·6%). The acid dissolved in alkali to give a yellow solution with a green fluorescence; its solution in concentrated sulphuric acid was pink with a brilliant yellowish-green fluorescence. The *methyl* ester crystallised from methyl alcohol in yellow needles, m. p. 167—168° (Found: C, 79·1; H, 4·5. $C_{19}H_{12}O_3$ requires C, 79·2; H, 4·2%).

Oxidation of 10-*Methyl*meso*benzanthrone.*—The benzanthrone (10 g.) in nitrobenzene (100 c.c.) was refluxed with selenium dioxide (10 g.) for 12 hours. The nitrobenzene was removed from the filtered solution in steam and the aqueous solution, after being made alkaline with sodium carbonate, was filtered, the filtrate (*A*) being reserved. The dried residue (9 g.) was extracted with chloroform and the soluble fraction (4 g.), containing 32% of aldehyde (estimated as the semicarbazone), was oxidised with potassium permanganate in pyridine solution as described in the case of the 9-methyl derivative (p. 211). The acid so obtained, together with that isolated from the alkaline solution (*A*) (in all 2·1 g.), was converted into the ethyl ester, which after being chromatographed, crystallised from alcohol in yellow needles, m. p. 133—136°. The acid, regenerated from the ester by hydrolysis with methyl-alcoholic potassium hydroxide solution, was esterified by diazomethane in dioxan solution. The methyl ester, after crystallisation from methyl alcohol, had m. p. 166—168°, both alone and in admixture with the methyl ester described above (Found: C, 79·1; H, 4·1%). Hydrolysis of the pure methyl ester gave the acid, which crystallised from acetic acid or nitrobenzene in yellow needles, m. p. 324—326° (Found: C, 79·1; H, 3·8%). This acid also resulted in very poor yield by the oxidation of 10-methyl-*meso*benzanthrone with nitrobenzene and alkali.

meso*Benzanthrone-4-carboxylic Acid.*—A mixture of 4-methyl*meso*benzanthrone (7 g.), nitrobenzene (50 c.c.), and potassium hydroxide (7 g.) was heated at 140—150° for 30 minutes (mechanical stirring). On cooling, a sparingly soluble potassium salt separated; this was collected, washed with nitrobenzene, and dissolved in hot water (charcoal), and the acid (5·6 g.) separated from the acidified solution. After crystallisation from nitrobenzene the acid was esterified through the acid chloride, and the ester chromatographed on alumina from a benzene solution and eluted with alcohol. *Ethyl* meso*benzanthrone-4-carboxylate* crystallised from alcohol in fine yellow needles, m. p. 134—135° (Found: C, 79·3; H, 4·8%), largely depressed by the ethyl ester, m. p. 137—139°, of the 9-carboxylic acid. The 4-carboxylic acid, obtained by hydrolysis of the ethyl ester, crystallised from nitrobenzene in yellow needles, m. p. 314—315° (Found: C, 78·8; H, 3·4%). Its deep red solution in sulphuric acid was not fluorescent, but the yellow alkaline solution showed a yellowish-green fluorescence. The *methyl* ester crystallised from methyl alcohol in yellow needles, m. p. 215—216° (Found: C, 79·2; H, 4·4%).

Condensation of Anthraquinone-1-carboxyamide and Glycerol. meso*Benzanthrone-8- and -11-carboxylic Acids.*—A mixture of the amide (15 g.), glycerol (40 c.c.), aniline (10 c.c.), and copper bronze (6 g.) in sulphuric acid (750 c.c.; 90%; $d^{15°}$ 1·820) was heated at 95—100° for 30 minutes (mechanical stirring). The solution became deep red and had a green fluorescence. The cooled solution was poured into water, and the precipitated solid collected and extracted with hot aqueous sodium carbonate. The insoluble residue (*X*) was reserved. The alkaline solution after digestion with charcoal was acidified, a black tar being precipitated. The supernatant liquor was decanted, and the residue extracted with boiling acetic acid (100 c.c.), the insoluble fraction being discarded. The filtrate (charcoal) deposited, on cooling, brownish-yellow needles (1·3 g.); a further quantity (1·1 g.) of less pure material was obtained after concentration of the solution. The acid in dioxan solution was esterified with diazomethane, and the methyl ester purified by passage through an alumina tower with benzene as the solvent. The pure ester remained as a lemon-yellow zone and was eluted by benzene containing a little methyl acetate. *Methyl* meso*benzanthrone-8-carboxylate* crystallised from methyl alcohol containing methyl acetate (10%) in brilliant yellow needles, m. p. 173·5—174·5° (Found: C, 79·1; H, 4·4. $C_{19}H_{12}O_3$ requires C, 79·2; H, 4·1%). Its solution in sulphuric acid was canary-yellow with a yellowish-green fluorescence.

The *acid*, prepared by hydrolysis of the ester with acetic–hydrochloric acids, alkaline hydrolysis yielding impure material, crystallised from chlorobenzene or acetic acid in yellow needles, m. p. 254—255° (Found: C, 78·9; H, 3·9. $C_{18}H_{10}O_3$ requires C, 78·8; H, 3·6%). Its solution in sulphuric acid was golden-yellow with a yellow fluorescence markedly different from that shown by the methyl ester; its solution in alkali was yellow with a green fluorescence.

For its oxidation to anthraquinone-1 : 5-dicarboxylic acid, chromic acid (1 g.) in acetic acid (5 c.c.) was added gradually to a boiling solution of the acid (0·5 g.) in acetic acid (35 c.c.). On completion of the oxidation sulphuric acid (1·5 g.) was added, the solution evaporated to dryness, the chromium sulphate dissolved in water, the oxidation acid collected and dissolved in concentrated sulphuric acid, and the solution poured into water; the precipitated acid was collected, dissolved in aqueous ammonia, and reprecipitated from the filtered solution. The anthraquinone acid (0·3 g.), which now separated as a crystalline solid, was esterified through the acid chloride, and the ethyl ester passed through an alumina tower, chloroform being used as the solvent. The chromatogram was colourless apart from a small ring at the top which showed a bright green fluorescence in the mercury lamp. The purified ester crystallised from alcohol in long needles, m. p. 153—154°, after slight softening (Found: C, 67·6; H, 4·8. Calc. for $C_{20}H_{16}O_6$: C, 68·1; H, 4·5%). Ethyl anthraquinone-1 : 5-dicarboxylate prepared from 1 : 5-dichloroanthraquinone (Coulson, J., 1930, 1931) crystallised from ethyl

alcohol or acetic acid in needles, m. p. 149—151°, not raised by further crystallisation. In admixture with the ester from the oxidation acid the m. p. was 150—153°.

The condensation product (*X*) (p. 212) (10 g.), insoluble in alkali, crystallised from nitrobenzene (180 c.c.) (charcoal) in yellow needles, m. p. 312—314° on fairly rapid heating; on slow heating, decomposition much below this temperature was observed (Found: C, 78·9; H, 4·1. Calc. for $C_{18}H_{11}O_2N$: C, 79·1; H, 4·0%). This m. p. is somewhat lower than that recorded by Boyes, Grieve, and Rule (*loc. cit.*), but, as they observed, the melting is accompanied by decomposition and is not very characteristic. For hydrolysis the amide (5 g.) was dissolved in sulphuric acid (100 c.c.) and treated at 0° with sodium nitrite (1·4 g.), added during 1 hour (mechanical stirring). After a further hour the mixture was poured on ice and the solid was collected and digested with aqueous sodium carbonate; the residue (4·2 g.) consisted of the unchanged amide, m. p. 312—314° (Found: C, 79·3; H, 4·1; N, 5·3%). The red alkaline solution was cautiously acidified till the red colour was just discharged; the small yellow precipitate obtained dissolved in alkali to give a purple solution with a red fluorescence and was obviously the lactone of 1-hydroxy*meso*benzanthrone-11-carboxylic acid (Boyes, Grieve, and Rule, *loc. cit.*). The yellow filtrate was made acid to Congo-paper; the acid which separated was esterified in dioxan solution with diazomethane. Methyl *meso*benzanthrone-11-carboxylate, after passage through an alumina tower with benzene as the solvent, crystallised from methyl alcohol in yellow needles, m. p. 160—161°, both alone and in admixture with a specimen of the ester prepared from an authentic sample of the 11-carboxylic acid by the action of methyl alcohol on the acid chloride (Found: C, 78·9; H, 4·4. Calc. for $C_{19}H_{12}O_3$: C, 79·2; H, 4·1%). *meso*Benzanthrone-11-carboxylic acid, prepared from the ester by alkaline hydrolysis, crystallised from chlorobenzene or acetic acid in slender yellow needles, m. p. 267—268°, both alone and in admixture with the 11-carboxylic acid (Found: C, 79·0; H, 3·9. Calc. for $C_{18}H_{10}O_3$: C, 78·8; H, 3·6%). When the acid was moistened with sulphuric acid, a red colour developed, but a solution of the acid was deep yellow with a very intense golden fluorescence (cf. Rule, Pursell, and Barnett, *loc. cit.*); the alkaline solution of the acid was yellow with a brilliant greenish-yellow fluorescence.

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38. *Attempts to find New Antimalarials. Part XVIII. Derivatives of* m-*Phenanthroline.*

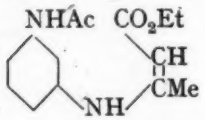
By WILLIAM O. KERMACK and WILLIAM WEBSTER.

Evidence is adduced that the compound formed by cyclisation of ethyl β-3-acetamidophenylaminocrotonate is *5-acetamido-4-hydroxy-2-methylquinoline* and not 7-acetamido-4-hydroxy-2-methylquinoline. *m*-Phenylenediamine condenses with ethyl oxaloacetate as with ethyl acetoacetate to yield the 7- and not the 5-aminoquinoline derivative. Various 2- and 4-hydroxy- and -chloro-derivatives of 5 : 6 : 2′ : 3′- and 7 : 8 : 2′ : 3′-pyridoquinoline have been prepared, and the latter condensed with β-diethylaminoethylamine and δ-diethylamino-α-methylbutylamine to yield the following bases: 4-(β-diethylaminoethylamino)- and 4-(δ-diethylamino-α-methylbutylamino)-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline; 4-(β-*diethylaminoethylamino*)-2-*methyl*-7 : 8 : 2′ : 3′-*pyridoquinoline* and 4-(δ-diethylamino-α-methylbutylamino)-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline; 2-(β-*diethylamino-ethylamino*)-4-*methyl*-7 : 8 : 2′ : 3′-*pyridoquinoline* and 2-(δ-diethylamino-α-methylbutylamino)-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline; 2-(β-diethylaminoethylamino)- and 2-(δ-diethylamino-α-methylbutylamino)-5 : 6 : 2′ : 3′-pyridoquinoline.

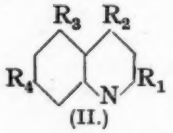
It is shown that the chloro-derivative formed by oxidation of *m*-phenanthroline methosulphate to *N*-methylphenanthrolone, followed by treatment of the latter with phosphorus oxychloride and pentachloride, is 2-chloro-5 : 6 : 2′ : 3′ -pyridoquinoline.

BACKEBERG (J., 1935, 1568) prepared ethyl β-3-acetamidophenylaminocrotonate (I) by the condensation of *m*-aminoacetanilide and ethyl acetoacetate, but he states that he was unable to effect its cyclisation by the method of Conrad and Limpach to 5- or 7-acetamido-4-hydroxy-2-methylquinoline. It has now been found possible to isolate from the product obtained by introducing the above compound into paraffin at 260°, a small yield of a crystalline product which in all probability is *5-acetamido-4-hydroxy-2-methylquinoline* (II; R_1 = Me, R_2 = OH, R_3 = NHAc, R_4 = H). The reason for attributing to it this structure and not that of the isomeric 7-acetamido-derivative (II; R_1 = Me, R_2 = OH, R_3 = H, R_4 = NHAc), is the following. On hydrolysis, the compound yields an amino-4-hydroxy-2-methylquinoline, which when subjected to the Skraup synthesis is converted into *4-hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline* (III; R_1 = Me, R_2 = OH) or 4-hydroxy-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (IV; R_1 = Me, R_2 =

OH). The latter of these two compounds has been prepared by Hazlewood, Hughes, and Lions (*J. Proc. Roy. Soc. N.S. Wales*, 1937—38, **71**, 472) from 5-aminoquinoline and acetoacetic ester, and is



(I.)



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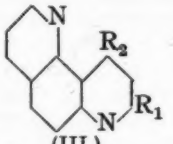

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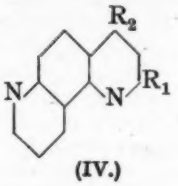


(IV.)

unmelted at 345°. We have repeated this synthesis and find that the m. p. is 395°, with previous darkening and sublimation at 300°. Furthermore, the *4-chloro-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* (IV; R_1 = Me, R_2 = Cl) prepared from this compound by the action of phosphorus oxychloride and phosphorus pentachloride melts at 190°, and that from the new compound at 140°. It follows that the latter must be derived from *5-amino-4-hydroxy-2-methylquinoline* (II; R_1 = Me, R_2 = OH, R_3 = NH_2, R_4 = H). The possibility that the new compound produced by the Skraup reaction is 4-hydroxy-2-methyl-7 : 6 : 2′ : 3′-pyridoquinoline, formed from the 7-aminoquinoline derivative by addition of a pyridine ring so as to form a linear instead of an angular structure, may be neglected in view of the large mass of evidence which shows that an angular structure is formed in preference to a linear one when both are possible products of reaction.

Various workers have shown (cf. Besthorn and Byvanck, *Ber.*, 1898, **31**, 796; Capps and Hamilton, *J. Amer. Chem. Soc.*, 1938, **60**, 2104) that, when *m*-phenylenediamine is heated with ethyl acetoacetate in a sealed tube or an autoclave, 7-amino-2-hydroxy-4-methylquinoline (II; R_1 = OH, R_2 = Me, R_3 = H, R_4 = NH_2) is formed. Here ring closure takes place in a direction different from that found above. The fact that one amino-group remains free throughout the reaction and is not acetylated may account for the difference, though the different orientation of the methyl and the hydroxyl group in the resulting compound may also play some part. It is unnecessary to use a closed vessel; if the components are gently refluxed on a sand-bath until the mixture solidifies, a 60% yield of the product is obtained. The application of the Skraup synthesis to 7-amino-2-hydroxy-4-methylquinoline yields *2-hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* (IV; R_1 = OH, R_2 = Me), from which *2-chloro-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* (IV; R_1 = Cl, R_2 = Me) is readily obtained by treatment with phosphorus oxychloride and pentachloride in a sealed tube at 120°.

When *m*-phenylenediamine is heated with ethyl oxaloacetate, ethyl 5 (or 7)-amino-2-hydroxyquinoline-4-carboxylate (II; R_1 = OH, R_2 = CO_2Et, R_3 = NH_2 or H, R_4 = H or NH_2) is obtained. On the analogy of the reaction with ethyl acetoacetate, the second of these two possible formulæ is the more probable. This view is confirmed in the following manner. The ester is hydrolysed to yield an amino-2-hydroxyquinoline-4-carboxylic acid, from which, on decarboxylation, an amino-2-hydroxyquinoline is obtained. That this is definitely 7-amino-2-hydroxyquinoline is shown by the fact that it is also obtained by oxidising 7-nitroquinoline with sodium hypochlorite according to the method of Capps and Hamilton (*loc. cit.*) to 7-nitro-2-hydroxyquinoline and reducing the latter. The amino-group must therefore be in the 7-position in the above compounds.

When the Skraup reaction is carried out on 7-amino-2-hydroxyquinoline, 2-hydroxy-7 : 8 : 2′ : 3′-pyridoquinoline (IV; R_1 = OH, R_2 = H) is obtained, from which 2-chloro-7 : 8 : 2′ : 3′-pyridoquinoline (IV; R_1 = Cl, R_2 = H) is formed by the action of phosphorus oxychloride and pentachloride.

By a similar series of reactions, 5-nitroquinoline may be converted into 5-nitro- and 5-amino-2-hydroxyquinoline (cf. Capps and Hamilton, *loc. cit.*). The application of the Skraup reaction to the latter compound results in the formation of *2-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline* (III; R_1 = OH, R_2 = H), from which the corresponding *2-chloro-5 : 6 : 2′ : 3′-pyridoquinoline* (III; R_1 = Cl, R_2 = H) is obtained by the action of phosphorus oxychloride and pentachloride.

2-Hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline is mentioned in the literature as being obtained as a by-product when *m*-nitroaniline is subjected to the Skraup reaction (La Coste, *Ber.*, 1883, **16**, 674). Later work (cf. Matsumura, *J. Amer. Chem. Soc.*, 1930, **52**, 3974; Sucharda and Mazonski, *Ber.*, 1936, **69**, 2719) has, however, shown that the compound in question is almost certainly 8-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline. It melts at 159—160° and so is different from 2-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline now synthesised. This is in keeping with the view that the hydroxy-group is in the 8-position.

According to D.R.-P. 654,444 the oxidation of *m*-phenanthroline (5 : 6 : 2′ : 3′- or 7 : 8 : 2′ : 3′-pyridoquinoline) methosulphate by alkaline potassium ferricyanide yields a *N*-methylphenanthrolone, from which by treatment with a mixture of phosphorus oxychloride and pentachloride, a 2-chlorophenanthroline

is obtained, the m. p. of which is given as 151°. The precise constitutions of these two compounds do not seem so far to have been determined; it is clear that the first might be either 2-keto-1-methyl-1 : 2-dihydro-5 : 6 : 2′ : 3′-pyridoquinoline or 2-keto-1-methyl-1 : 2-dihydro-7 : 8 : 2′ : 3′-pyridoquinoline, and the second might be the 2-chloro-derivative of either 5 : 6 : 2′ : 3′- or 7 : 8 : 2′ : 3′-pyridoquinoline, according to which of the two nitrogen atoms of *m*-phenanthroline reacts with methyl sulphate. It is now shown that the chloropyridoquinoline obtained by this series of reactions is identical with 2-chloro-5 : 6 : 2′ : 3′-pyridoquinoline synthesised by the method described in the last paragraph, and distinct from the isomeric 2-chloro-7 : 8 : 2′ : 3′-pyridoquinoline. The methosulphate is therefore 1-methyl-5 : 6 : 2′ : 3′-pyridoquinolinium methyl sulphate, and the intermediate product is 2-keto-1-methyl-1 : 2-dihydro-5 : 6 : 2′ : 3′-pyridoquinoline.

In preparing the methosulphate, it was found that freshly distilled *m*-phenanthroline and methyl sulphate, refluxed in methyl-alcoholic solution, yielded a crystalline salt of the original base, $C_{12}H_8N_2$,$MeHSO_4$. When the freshly distilled base and methyl sulphate were warmed together, the product was not homogeneous, but fractional crystallisation gave the true methosulphate, m. p. 168—169° (the patent gives 171°). It seems that in presence of *m*-phenanthroline, methyl sulphate undergoes hydrolysis with peculiar ease, unless special precautions are taken to exclude all traces of water.

The bases listed in the summary were prepared by heating the appropriate chloro-compounds with β-diethylaminoethylamine or δ-diethylamino-α-methylbutylamine in presence of a trace of copper bronze.

Experimental.

5-Acetamido-4-hydroxy-2-methylquinoline.—Ethyl β-3-acetamidophenylaminocrotonate (10 g.), prepared by heating on a boiling water-bath an equimolecular mixture of ethyl acetoacetate and *m*-aminoacetanilide containing a drop of concentrated hydrochloric acid (cf. Coffey, Thomson, and Wilson, J., 1936, 856) and scratching the cooled product with light petroleum, was added to medicinal paraffin (400 c.c.) preheated to 270°. Ethyl alcohol was evolved and a heavy brown oil separated. When this had cooled, light petroleum was added, and a small quantity of a yellow crystalline product removed by filtration. The bulk of the product, however, remained in the flask as a sticky brown oil; this was washed with light petroleum and extracted several times with boiling water, from which, on cooling, *5-acetamido-4-hydroxy-2-methylquinoline* separated; recrystallised from hot water, it formed yellow needles (2·5 g.), m. p. 236°, soluble in alcohol and methyl alcohol, but insoluble in light petroleum and benzene (Found: C, 66·6; H, 5·8. $C_{12}H_{12}O_2N_2$ requires C, 66·7; H, 5·6%). The compound is soluble in cold dilute sodium hydroxide solution, but only slightly soluble in cold dilute mineral acid.

5-Amino-4-hydroxy-2-methylquinoline.—5-Acetamido-4-hydroxy-2-methylquinoline (5 g.) was boiled with 33% hydrochloric acid (100 c.c.) for 30 minutes. *5-Amino-4-hydroxy-2-methylquinoline*, precipitated when the cooled filtered solution was basified, crystallised from hot water in pale yellow needles (3·8 g.), m. p. 210° (Found: N, 16·2. $C_{10}H_{10}ON_2$ requires N, 16·1%). This compound is soluble in alcohol and methyl alcohol, slightly soluble in benzene, and insoluble in light petroleum. It is soluble in dilute mineral acid but only slightly soluble in dilute sodium hydroxide solution.

4-Hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline.—5-Amino-4-hydroxy-2-methylquinoline (4·1 g.), arsenic acid (3·4 g.), glycerol (7·1 g.), and concentrated sulphuric acid (6·4 g.) were refluxed for 5—6 hours; the dark brown solution then no longer gave the diazo-reaction. The cooled product was diluted with water, filtered, and basified with sodium hydroxide solution. The brown precipitate was collected and dissolved in dilute hydrochloric acid; the solution was almost neutralised with sodium hydroxide solution and filtered from the tarry precipitate. On basification *4-hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline* (30 g.) separated; recrystallised from aqueous alcohol, it formed colourless needles, m. p. 142° (Found: N, 13·6. $C_{12}H_{10}ON_2$ requires N, 13·3%), insoluble in cold but slightly soluble in hot water, slightly soluble in alcohol, methyl alcohol and benzene, but insoluble in light petroleum. It was soluble in dilute acid and to a less extent in dilute sodium hydroxide solution.

4-Chloro-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline.—4-Hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline (1 g.), phosphorus pentachloride (1 g.), and phosphorus oxychloride (8 c.c.) were refluxed for 3 hours. The excess of phosphorus oxychloride was removed in a vacuum, and the residue extracted with hot water. On basification of the filtered aqueous solution a cream-coloured precipitate of *4-chloro-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline* was obtained; recrystallised from aqueous alcohol, it formed long colourless needles (0·8 g.), m. p. 140° (Found: C, 67·9; H, 3·6. $C_{12}H_9N_2Cl$ requires C, 68·3; H, 3·9%), soluble in light petroleum, benzene and alcohol, insoluble in cold but slightly soluble in boiling water, from which, on cooling, it separated in colourless needles. It was soluble in dilute mineral acid but insoluble in dilute alkali solution.

4-Chloro-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline, similarly obtained (5 hours' heating) from 4-hydroxy-2-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (1 g.), crystallised from alcohol in long colourless needles (0·85 g.), m. p. 190° (Found: C, 68·0; H, 3·9%), insoluble in cold and very slightly soluble in hot water, moderately soluble

in benzene and light petroleum, but insoluble in acetone. It was soluble in dilute mineral acid but insoluble in dilute sodium hydroxide solution.

2-Hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline.—7-Amino-2-hydroxy-4-methylquinoline (5 g.), arsenic acid (4·15 g.), glycerol (8·5 g.), and concentrated sulphuric acid (7·8 g.) were refluxed for 6 hours, and the cooled solution diluted with water (2 vols.), filtered, and exactly neutralised with sodium hydroxide solution; a light brown precipitate then separated. This was dissolved in warm 50% acetic acid, and the filtered solution made alkaline with sodium hydroxide solution. The insoluble tar was removed and when the filtrate was exactly neutralised with hydrochloric acid, *2-hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline* separated (3·5 g.); it crystallised from alcohol in small, light yellow plates, m. p. 318° with previous sublimation and darkening at about 300° (Found : N, 13·4. $C_{13}H_{10}ON_2$ requires N, 13·3%). This compound is insoluble in water and most of the common organic solvents, soluble to a small extent in hot alcohol and methyl alcohol. The alcoholic solution of the base exhibits a bluish-purple fluorescence which changes to green on the addition of hydrochloric acid but disappears on the addition of sodium hydroxide. No fluorescence was observed in either acid or alkaline aqueous solution. A small sample of compound in a very pure condition may be obtained by sublimation, but this method entails considerable loss by decomposition.

2-Chloro-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline, prepared by heating 2-hydroxy-4-methyl-7 : 8 : 2′ : 3′-pyridoquinoline (3·9 g.) with phosphorus pentachloride (3·9 g.) and oxychloride (16 c.c.) in a sealed tube for 3 hours at 120°, and isolated in the same way as the two preceding chloro-compounds, crystallised from aqueous alcohol in colourless needles (3·4 g.), m. p. 161° (Found : C, 68·3; H, 3·7. $C_{13}H_9N_2Cl$ requires C, 68·3; H, 3·9%), soluble in dilute mineral acid but insoluble in dilute sodium hydroxide solution, slightly soluble in alcohol and methyl alcohol, moderately easily soluble in hot light petroleum, from which it crystallised on cooling, soluble in benzene but insoluble in acetone. Its alcoholic solution exhibited a bluish-violet fluorescence.

Ethyl 7-Amino-2-hydroxyquinoline-4-carboxylate.—*m*-Phenylenediamine (10·8 g.), freshly distilled in a vacuum, and ethyl oxaloacetate (18·8 g.), freshly prepared from its sodium salt, were refluxed on the sand-bath. After 1 hour the crystalline mass of *ethyl 7-amino-2-hydroxyquinoline-4-carboxylate* was cooled, washed with methyl alcohol, and recrystallised from alcohol, forming long yellow needles (8 g.), m. p. 262° (Found : C, 61·8; H, 4·9. $C_{12}H_{12}O_3N_2$ requires C, 62·1; H, 5·2%), slightly soluble in water, methyl alcohol, benzene, and light petroleum. It dissolved in hot dilute aqueous sodium hydroxide and in dilute acid, giving a colourless and a yellow solution respectively.

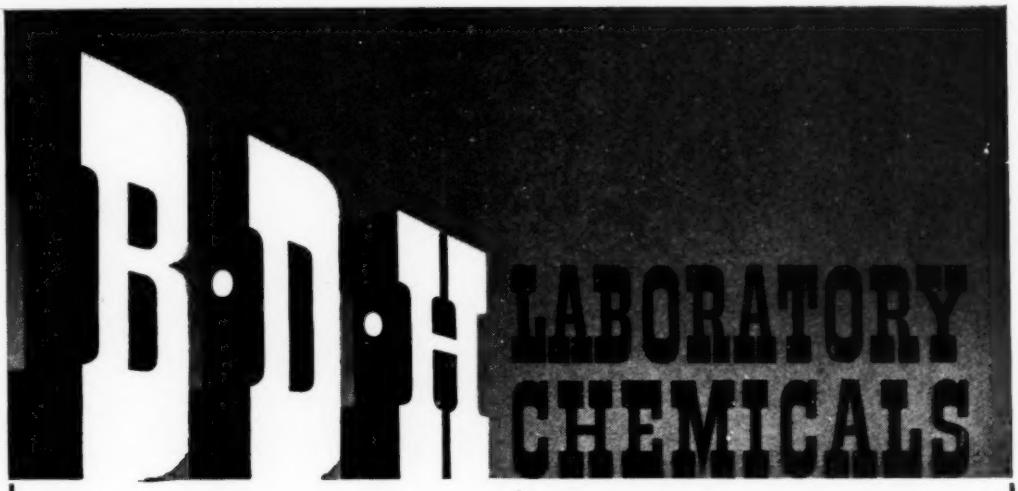
7-Amino-2-hydroxyquinoline-4-carboxylic Acid.—The ethyl ester (6·0 g.) and an alcoholic solution of potassium hydroxide (60 c.c. of 5%) were refluxed for 20 minutes. Potassium 7-amino-2-hydroxyquinoline-4-carboxylate separated in light brown crystals; a further quantity was obtained by the addition of acetone. Recrystallised from aqueous acetone, the salt formed long colourless needles, m. p. 394° (decomp.), the yield being almost theoretical. It was readily soluble in cold water (green fluorescence), slightly soluble in hot alcohol (blue fluorescence) and soluble in methyl alcohol. When an aqueous solution of the salt was made very slightly acid, *7-amino-2-hydroxyquinoline-4-carboxylic acid* separated as a light brown precipitate (soluble in excess of the mineral acid); it crystallised from alcohol in small light needles, which began to decompose at 345° but were unmelted at 400° (Found : C, 58·5; H, 3·8. $C_{10}H_8O_3N_2$ requires C, 58·8; H, 3·9%). This acid was only sparingly soluble in hot alcohol and very sparingly soluble in most of the usual organic solvents. Its alcoholic solution exhibited a strong green fluorescence; no fluorescence was observed in hydrochloric acid.

7-Amino-2-hydroxyquinoline.—The preceding acid (2 g.), copper powder (1·0 g.), and quinoline (20 c.c.) were refluxed for 3 hours. Water was added to the hot filtered solution, and the quinoline removed by steam-distillation. 7-Amino-2-hydroxyquinoline, which separated from the concentrated, cooled aqueous solution, crystallised from hot water in white needles (0·5 g.), m. p. 292—293°, not depressed by a sample prepared by the reduction of 7-nitro-2-hydroxyquinoline (Capps and Hamilton, *loc. cit.*).

2-Chloro-7 : 8 : 2′ : 3′-pyridoquinoline.—7-Amino-2-hydroxyquinoline (1 g.), arsenic acid (0·8 g.), glycerol (1·8 g.), and concentrated sulphuric acid (1·6 g.) were refluxed for 3 hours, and the product diluted with water, filtered, and neutralised with sodium carbonate solution. The 2-hydroxy-7 : 8 : 2′ : 3′-pyridoquinoline was recrystallised from alcohol, forming pale yellow needles, m. p. 290° after decomposition and sublimation at 275°. This slightly impure compound (0·5 g.) was refluxed with phosphorus oxychloride (4 c.c.) and pentachloride (0·5 g.) for 3 hours, and the product treated in the usual way. *2-Chloro-7 : 8 : 2′ : 3′-pyridoquinoline* separated from aqueous alcohol in small colourless needles (0·35 g.), m. p. 160° (Found : C, 66·6; H, 3·1. $C_{12}H_7N_2Cl$ requires C, 67·1; H, 3·3%), very slightly soluble in water, soluble in alcohol, insoluble in light petroleum, soluble in dilute mineral acids but insoluble in sodium hydroxide solution.

2-Hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline (3·0 g.), prepared from 5-amino-2-hydroxyquinoline (4·0 g.), arsenic acid (3·5 g.), glycerol (7·2 g.), and concentrated sulphuric acid (6·6 g.) (3 hours' refluxing) and isolated as in the case of 4-hydroxy-2-methyl-5 : 6 : 2′ : 3′-pyridoquinoline, was sublimed at 290° and then recrystallised from alcohol, forming colourless needles, m. p. 315° after decomposition and sublimation at 290° (Found : C, 72·9; H, 4·3. $C_{12}H_8ON_2$ requires C, 73·4; H, 4·1%), insoluble in water, slightly soluble in most organic solvents, soluble in dilute mineral acids and in dilute sodium hydroxide solution.

2-Chloro-5 : 6 : 2′ : 3′-pyridoquinoline (0·85 g.), prepared from 2-hydroxy-5 : 6 : 2′ : 3′-pyridoquinoline (1·0 g.), phosphorus pentachloride (1·0 g.), and oxychloride (8 c.c.), crystallised from aqueous alcohol in colour-



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